INVENTOR SEARCH

=> fil capl
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FILE COVERS 1907 - 21 Mar 2007 VOL 146 ISS 13
FILE LAST UPDATED: 20 Mar 2007 (20070320/ED)

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=> => => d que l2
L2 1 SEA FILE=CAPLUS ABB=ON US2004-763935/AP

=> s l2 or (l2 and l32,l30)
L33 1 L2 OR (L2 AND (L32 OR L30))

=> d ibib ed abs hitseq l33 1

Applicant

L33 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:117793 CAPLUS Full-text
DOCUMENT NUMBER: 138:153832
TITLE: Preparation of corticotropin-releasing factor (CRF) analogs as CRF receptor type 1 (CRFR1) selective ligands
INVENTOR(S): Rivier, Jean E. F.; Vale, Wylie W., Jr.; Perrin, Marilyn H.; Guylas, Jozsef
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003011823	A2	20030213	WO 2002-US24238	20020730

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH,

PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

CA 2455223	A1	20030213	CA 2002-2455223	20020730
JP 2005510458	T	20050421	JP 2003-517015	20020730
EP 1572679	A2	20050914	EP 2002-752639	20020730
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK				
US 2004204564	A1	20041014	US 2004-763935	20040122 <--
PRIORITY APPLN. INFO.:			US 2001-309504P	P 20010801
			WO 2002-US24238	W 20020730

OTHER SOURCE(S): MARPAT 138:153832
ED Entered STN: 14 Feb 2003
AB Corticotropin-releasing factor (CRF) peptides Y1-Pro-Pro-R6-Ser-R8-Asp-R10-R11-D-Phe-R13-R14-R15-Arg-R17-R18-R19-R20-R21-R22-R23-R24-R25-R26-R27-R28-R29-Gln-Glu-R32-R33-R34-Arg-R36-R37-R38-R39-R40-R41-NH2 (Y1 is acyl having < 15 carbon atoms or radioiodinated tyrosine; the R groups represent various amino acid residues which are defined) or their nontoxic salts are claimed for selective binding to CRFR1. Thus, cyclo(31-34)(Ac-Pro4,D-Phe12,Nle21,38,Glu31,Lys34)-r/hCRF(4-41) was prepared by the solid-phase method and shown to bind hCRFR1 with high affinity and significantly lowered blood pressure when administered peripherally.
IT **496031-18-6P 496031-20-0P 496031-22-2P**
496031-24-4P 496031-25-5P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of corticotropin-releasing factor (CRF) analogs as CRF receptor
type 1 (CRFR1) selective ligands)
RN 496031-18-6 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-L-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 496031-20-0 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-2-methylalanyl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 496031-22-2 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-

L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-D-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 496031-24-4 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-D-alanyl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 496031-25-5 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-L-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-L-isoleucyl- (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **496031-14-2P 496031-15-3P 496031-16-4P**
496031-17-5P 496031-19-7P 496031-21-1P
496031-23-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of corticotropin-releasing factor (CRF) analogs as CRF receptor
type 1 (CRFR1) selective ligands)
RN 496031-14-2 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-L-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-L-isoleucyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

Claim 3a

NTE modified

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHS KRKLXEII

RN 496031-15-3 CAPLUS
CN L-Leucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-

Claim 3b

CM2

histidyl-L-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-L-isoleucyl-2-methyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHS KRKLXEIL

RN 496031-16-4 CAPLUS
CN L-Leucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-2-methylalanyl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-L-isoleucyl-2-methyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

Claims 3(c)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHX KRKLXEIL

RN 496031-17-5 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-L-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHS KRKLXELI

RN 496031-19-7 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-2-methylalanyl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHX KRKLXELI

RN 496031-21-1 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-D-seryl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHS KRKLXELI

RN 496031-23-3 CAPLUS
CN L-Isoleucinamide, 1-acetyl-L-prolyl-L-prolyl-L-isoleucyl-L-seryl-L-leucyl-L-α-aspartyl-L-leucyl-L-threonyl-D-phenylalanyl-L-histidyl-L-leucyl-L-leucyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-2-methyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-α-glutamyl-L-histidyl-D-alanyl-L-lysyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-2-methyl-L-leucyl-, (28→31)-lactam (9CI) (CA INDEX NAME)

NTE modified (modifications unspecified)

SEQ 1 PPISLDLTFH LLREVLEXAR AEQLAQQEHA KRKLXELI

SEQUENCE SEARCH (CLAIM 1)

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=> fil reg; d que l13
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STRUCTURE FILE UPDATES:   19 MAR 2007  HIGHEST RN 927525-36-8
DICTIONARY FILE UPDATES:  19 MAR 2007  HIGHEST RN 927525-36-8

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      NOTE:  IN THE REGISTRY FILE, "CML" IS REPRESENTED AS "L" (LEUCINE) IN
               SEQUENCES, WITH A "MODIFIED" COMMENT IN THE NOTE FIELD


=> fil capl; d que l32
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FILE COVERS 1907 - 21 Mar 2007  VOL 146 ISS 13
FILE LAST UPDATED: 20 Mar 2007  (20070320/ED)

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                'L][L'NLE'Y]['NLE'ML][E'AIB'D][I'AIB'LTEAV'NLE'F'NVA'GQ][A'AIB'
                ILGV'NLE'F'NVA'Q]/SQSP
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=> s l32 not l2
L34           0 L32 NOT L2
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STRUCTURE SEARCH REPRESENTING E*HSK*, ALLOWING FOR CONSERVATIVE SUBSTITUTION OF ANY OF THESE 4 AMINO ACIDS,
ALSO OPEN TO FURTHER SUBSTITUTION ALONG THE PEPTIDE BACKBONE
=> fil reg; d stat que l27
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DICTIONARY FILE UPDATES: 19 MAR 2007 HIGHEST RN 927525-36-8

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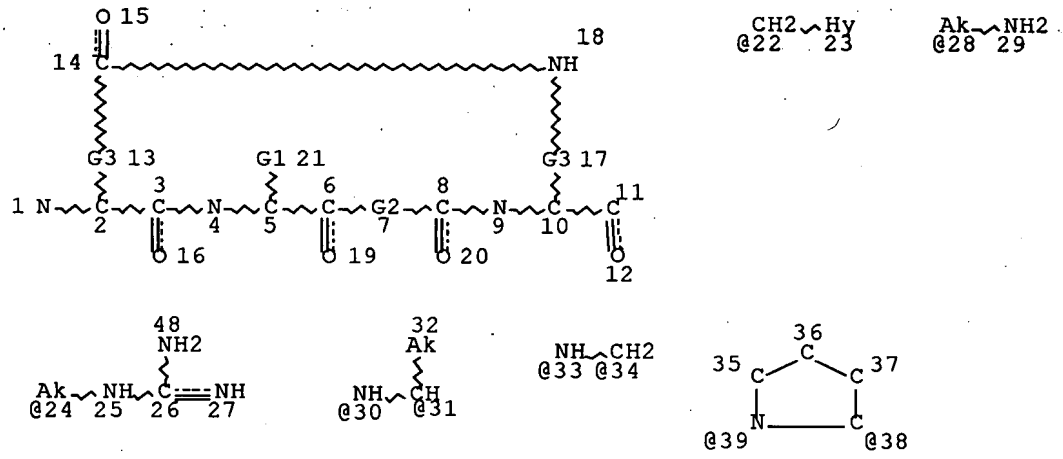
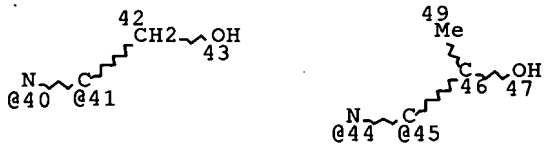
L24 STR



Page 1-A



Page 2-A
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CONNECT IS E2  RC AT  24
CONNECT IS E2  RC AT  28
CONNECT IS E1  RC AT  32
DEFAULT MLEVEL IS ATOM
GGCAT   IS MCY  UNS  AT  23
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E3 C  E2 N  AT  23

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  49

STEREO ATTRIBUTES: NONE
L27          21 SEA FILE=REGISTRY SSS FUL L24

100.0% PROCESSED   49524 ITERATIONS                          21 ANSWERS
SEARCH TIME: 00.00.03


=> fil capl; d que nos l30
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L24             STR
L27          21 SEA FILE=REGISTRY SSS FUL L24
L30          14 SEA FILE=CAPLUS ABB=ON  L27


=> s l30 not l2
L35          14 L30 NOT L2

=> d ibib ed abs hitstr 1-14; fil hom
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L35 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1127405 CAPLUS Full-text
DOCUMENT NUMBER: 142:69459
TITLE: Peptides that modulate the glucagon response and uses thereof
INVENTOR(S): Peri, Krishna G.
PATENT ASSIGNEE(S): Theratechnologies Inc., Can.
SOURCE: PCT Int. Appl., 87 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004111078	A2	20041223	WO 2004-CA885	20040618
WO 2004111078	A3	20050317		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005124550	A1	20050609	US 2004-871885	20040618
PRIORITY APPLN. INFO.:			US 2003-479692P P	20030618

ED Entered STN: 24 Dec 2004

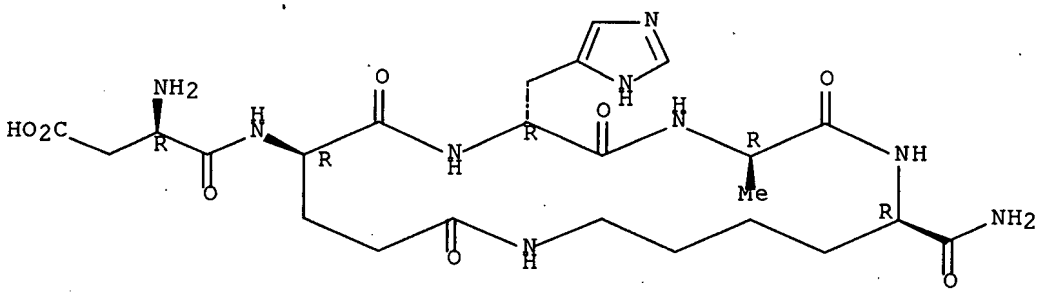
AB Peptides that modulate the glucagon response in a mammal are provided. The peptides comprise an amino acid sequence of between about 5 and about 10 amino acids in length that corresponds to the sequence of an extracellular membrane insertion region of a mammalian glucagon receptor, wherein at least one amino acid of the peptide has a D-configuration. Methods of preparing the peptides and the use of the peptides in the amelioration, treatment and/or prevention of glucagon-mediated conditions and diseases such as hyperglycemia, diabetes and obesity are also provided.

IT **811411-88-8**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(glucagon receptor-related peptides that modulate the glucagon response and uses thereof)

RN 811411-88-8 CAPLUS

CN D-Lysinamide, D-α-aspartyl-D-α-glutamyl-D-histidyl-D-alanyl-, (2→5)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:122201 CAPLUS Full-text
DOCUMENT NUMBER: 132:303582
TITLE: Design of Potent Dicyclic (4-10/5-8) Gonadotropin Releasing Hormone (GnRH) Antagonists
AUTHOR(S): Rivier, Jean E.; Struthers, R. Scott; Porter, John; Lahrichi, Sabine L.; Jiang, Guangcheng; Cervini, Laura A.; Ibea, Michel; Kirby, Dean A.; Koerber, Steven C.; Rivier, Catherine L.
CORPORATE SOURCE: Clayton Foundation Laboratories for Peptide Biology, The Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(5), 784-796
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 23 Feb 2000
AB With the ultimate goal of identifying a consensus bioactive conformation of GnRH antagonists, the compatibility of a number of side chain to side chain bridges in bioactive analogs was systematically explored. In an earlier publication, cyclo[Asp4-Dpr10]GnRH antagonists with high potencies in vitro and in vivo had been identified. Independently from Dutta et al. and based on structural considerations, the cyclic [Glu5-Lys8] constraint was also found to be tolerated in GnRH antagonists. We describe here a large number of cyclic (4-10) and (5-8) and dicyclic (4-10/5-8) GnRH antagonists optimized for affinity to the rat GnRH receptor and in vivo antiovulatory potency. The most potent monocyclic analogs were cyclo(4-10)[Ac-DNal1,DFpa2,DTrp3,Asp4,DArg6,Xaa10]GnRH with Xaa = D/LAgl (1, Ki = 1.3 nM) or Dpr (2, Ki = 0.36 nM), which completely blocked ovulation in cycling rats after s.c. administration of 2.5 μg at noon of proestrus. Much less potent were the closely related analogs with Xaa = Dbu (3, Ki = 10 nM) or cyclo(4-10)[Ac-DNal1,DFpa2,DTrp3,Glu4,DArg6,D/LAg l10]GnRH (4, Ki = 1.3 nM). Cyclo(5-8)[Ac-DNal1,DCpa2,DTrp3,Glu5,DArg6,Lys 8,DAla10]GnRH (13), although at least 20 times less potent in the AOA than 1 or 2 with similar GnRHR affinity (Ki = 0.84 nM), was found to be one of the most potent in a series of closely related cyclo(5-8) analogs with different bridge lengths and bridgehead chirality. The very high affinity of cyclo(5,5'-8)[Ac-DNal1,DCpa2,DPal3,Glu5(βAla),DArg6,(D or L)Agl,8DAla10]GnRH 14 (Ki = 0.15 nM) correlates well with its high potency in vivo (full inhibition of ovulation at 25 μg/rat). Dicyclo(4-10/5-8)[Ac-DNal1,DCpa2,DTrp3,Asp4,Glu5,DArg6,Lys8,Dpr10]GnRH (24, Ki = 0.32 nM) is one-fourth as potent as 1 or 2, in the AOA; this suggests that the introduction of the (4-10) bridge in 13, while having little effect on affinity, restores functional/conformational features favorable for stability and distribution. To further increase potency of dicyclic antagonists, the size and composition of the (5-8) bridge was varied. For example, the substitution of Xbb5' by Gly

(30, Ki = 0.16 nM), Sar (31, Ki = 0.20 nM), Phe (32, Ki = 0.23 nM), DPhe (33, Ki = 120 nM), Arg (36, Ki = 0.20 nM), Nal (37, Ki = 4.2 nM), His (38, Ki = 0.10 nM), and Cpa (39, Ki = 0.23 nM) in cyclo(4-10/5,5'-8)[Ac-DNal1,DCpa2,DPal3,Asp4,Glu5(Xbb5'),DAr g6,Dbu,8Dpr10]GnRH yielded several very high affinity analogs that were 10, ca. 10, 4, >200, 1, ca. 4, >2, and 2 times less potent than 1 or 2, resp. Other scaffolds constrained by disulfide (7, Ki = 2.4 nM; and 8, Ki = 450 nM), cyclo[Glu5-Aph8] (16, Ki = 20 nM; and 17, Ki = 0.28 nM), or cyclo[Asp5-/Glu5-/Asp5(Gly5')-Amp8] (19, Ki = 1.3 nM; 22, Ki = 3.3 nM; and 23, Ki = 3.6 nM) bridges yielded analogs that were less potent in vivo and had a wide range of affinities. The effects on biol. activity of substituting DCpa or DFpa at position 2, DPal or DTrp at position 3, and DArg, DNal, or DCit at position 6 are also discussed. Interestingly, monocyclo(5-8)[Glu5,DNal6,Lys8]GnRH (18, Ki = 1.0 nM) and dicyclo(4-10/5-8)[Asp4,Glu5,DNal6,Lys8,Dpr10]GnRH (28, Ki = 1.2 nM) contain the native N-terminal pGlu-His-Trp- and are antagonists with relatively high affinity but very low antagonist potency in vivo, illustrating an earlier observation that structural constraints alone may lead to partial agonism or competitive antagonism. Suggest very rigorous requirements for ligand/receptor recognition and binding as well as a distinct effect of some substitutions on pharmacokinetics.

IT **265094-13-1P 265094-14-2P 265094-16-4P**
265094-18-6P 265094-19-7P

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)

(dicyclic LH-RH antagonist design and ovulation-inhibiting activity and pharmacokinetics)

RN 265094-13-1 CAPLUS

CN D-Alaninamide, N-acetyl-3-(2-naphthalenyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridinyl)-D-alanyl-L-seryl-D-α-aspartyl-D-arginyl-L-leucyl-D-lysyl-L-prolyl-, (5→8)-lactam (9CI) (CA INDEX NAME)

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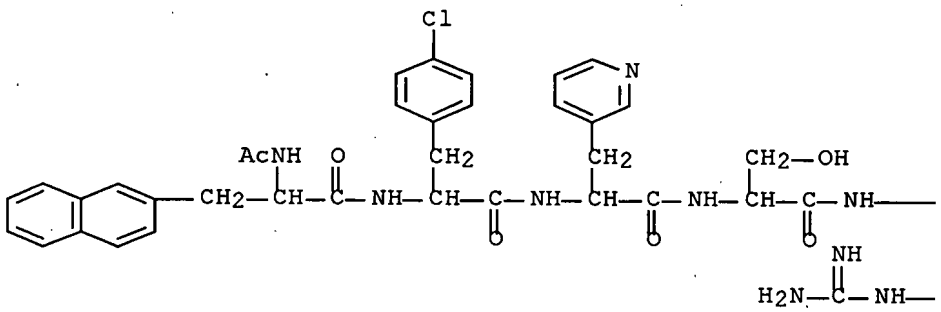

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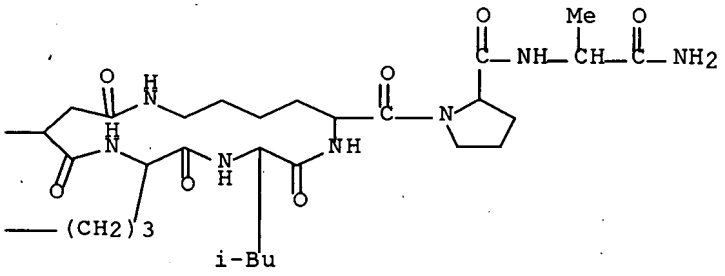

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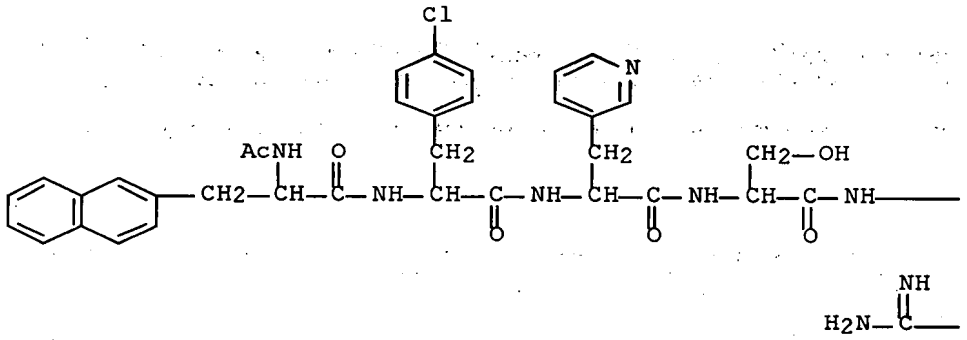
PAGE 1-A



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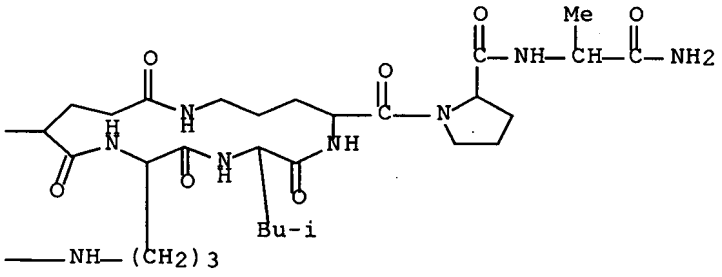

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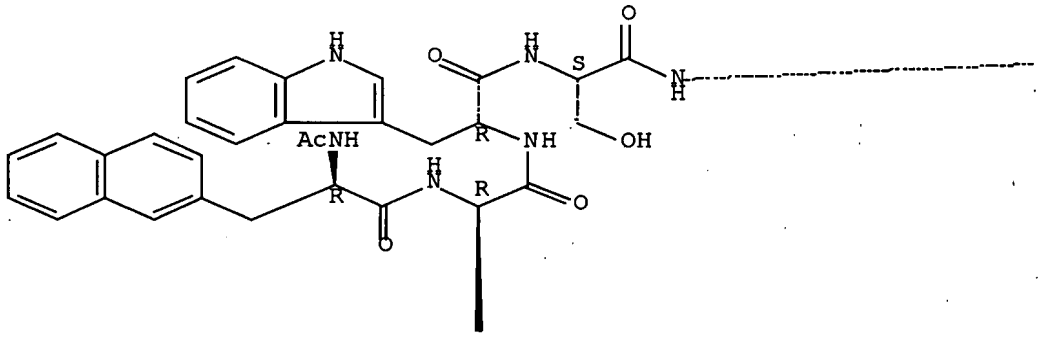
lysyl-L-prolyl-, (5→8)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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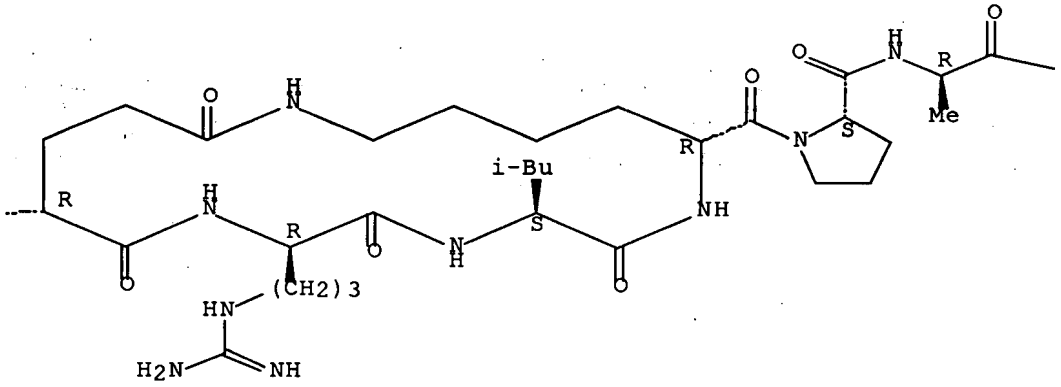

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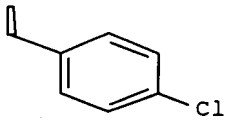

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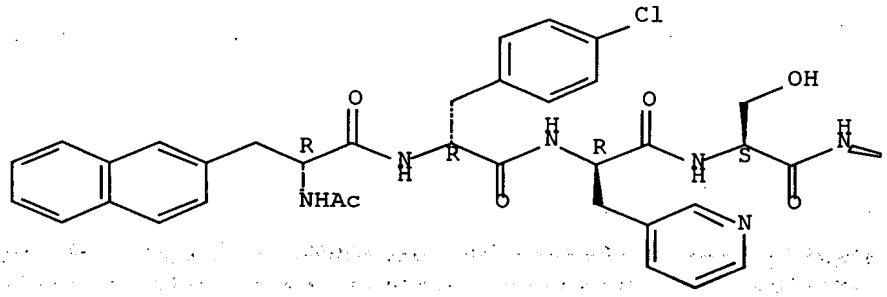
Absolute stereochemistry.

PAGE 1-A



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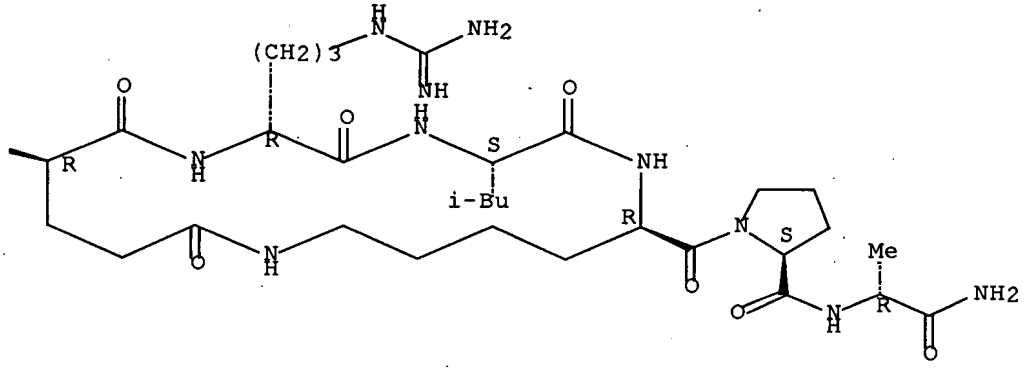

RN 265094-19-7 CAPLUS
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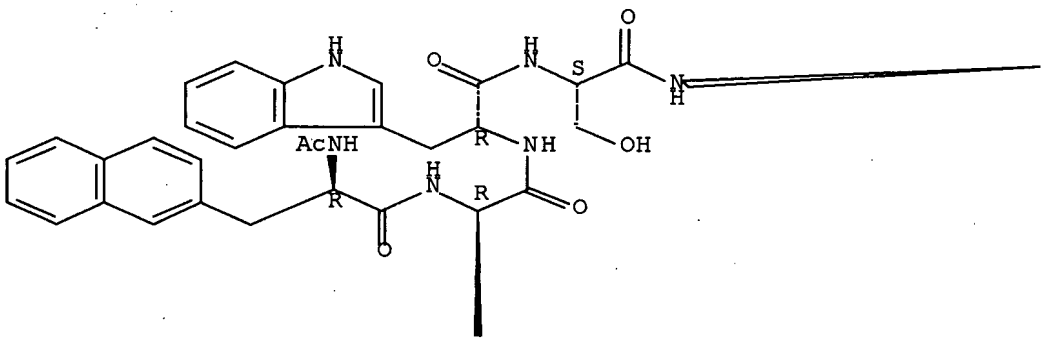
Absolute stereochemistry.

PAGE 1-A



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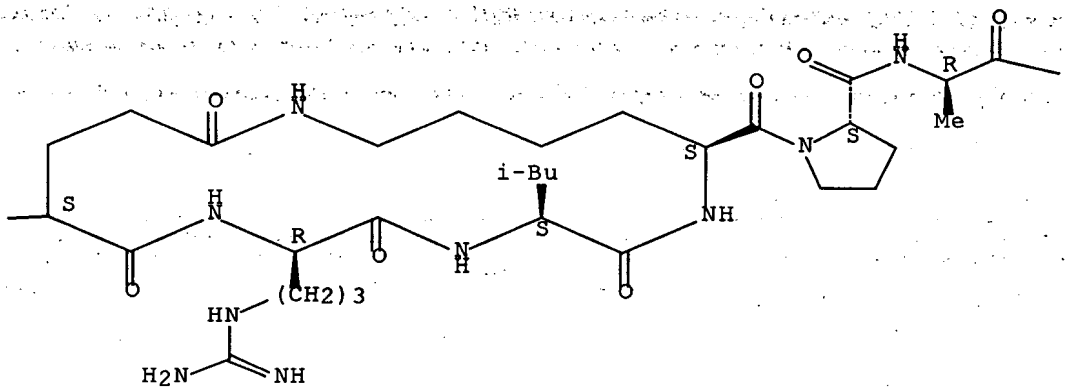

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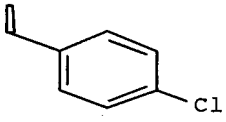

REFERENCE COUNT: 59 THERE ARE 59 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:85300 CAPLUS Full-text
DOCUMENT NUMBER: 128:123868
TITLE: Human Growth Hormone-Releasing Hormone hGHRH(1-29)-NH2: Systematic Structure-Activity Relationship Studies
AUTHOR(S): Cervini, Laura A.; Donaldson, Cynthia J.; Koerber, Steven C.; Vale, Wylie W.; Rivier, Jean E.
CORPORATE SOURCE: Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Medicinal Chemistry (1998), 41(5), 717-727
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 14 Feb 1998
AB Two complete and two partial structure-activity relationship scans of the active fragment of human growth hormone-releasing hormone, [Nle27]-hGHRH(1-29)-NH2, have identified potent agonists in vitro. Single-point replacement of each amino acid by alanine led to the identification of [Ala8]-, [Ala9]-, [Ala15]-, [Ala22]-, and [Ala28,Nle27]-hGHRH(1-29)-NH2 as being 2-6 times more potent than hGHRH(1-40)-OH (standard) in vitro. Nearly complete loss of potency was seen for [Ala1], [Ala3], [Ala5], [Ala6], [Ala10], [Ala11], [Ala13], [Ala14], and [Ala23], whereas [Ala16], [Ala18], [Ala24], [Ala25], [Ala26], and [Ala29] yielded equipotent analogs and [Ala7], [Ala12], [Ala17], [Ala20], [Ala21], and [Ala27] gave weak agonists with potencies 10-40% that of the standard The multiple-alanine-substituted peptides [MeTyr1,Ala15,22,Nle27]- hGHRH(1-29)-NH2 (29) and [MeTyr1,Ala8,9,15,22,28,Nle27]-hGHRH(1-29)-NH2 (30) released growth hormone 26 and 11 times, resp., more effectively than the standard in vitro. Individual substitution of the nine most potent peptides identified from the Ala series with the helix promoter α-aminoisobutyric acid (Aib) produced similar results, except for [Aib8] (doubling vs. [Ala8]), [Aib9] (halving vs. [Ala9]), and [Aib15] (10-fold decrease vs. [Ala15]). A series of cyclic analogs was synthesized having the general formula cyclo(25-29)[MeTyr1,Ala15,Xaa25,Nle27,Yaa29]-GHRH(1-29)-NH2, where Xaa and Yaa represent the bridgehead residues of a side-chain cystine or [i-(i+4)] lactam ring. The ring size, bridgehead amino acid chirality, and side-chain amide bond location were varied in this partial series to maximize potency. Application of lactam constraints in the C-terminus of GHRH(1-29)-NH2 identified cyclo(25-29)[MeTyr1,Ala15,DAsp25,Nle27,Orn29]- hGHRH(1-29)-NH2 (46) as containing the optimum bridging element (19-membered ring) in this region of the mol. This analog (46) was 17 times more potent than the standard Equally effective was an [i-(i+3)] constraint yielding the 18-membered ring cyclo(25-28)[MeTyr1,Ala15,Glu25,Nle,27Lys28]- hGHRH(1-29)-NH2 (51) which was 14 times more potent than the standard A complete [i-(i+3)] scan of cyclo(i,i+3)[MeTyr1,Ala15,Glui,Lys(I+3),Nle27]- hGHRH(1-29)-NH2 was then produced to test the effects of a Glu-to-Lys lactam bridge at all points in the peptide. Of the 26 analogs in the series, 11 had diminished potencies of less than 10% that of the agonist standard, 4 were weak agonists (15-40% relative potency), and 4 analogs were equipotent to the standard The 7 most potent analogs ranged in potency from 3 to 14 times greater than that of the standard and contained the [i-(i+3)] cycles between residues 4-7, 5-8, 9-12, 16-19, 21-24, 22-25, and 25-28. The combined results from these systematic studies allowed for an anal. of structural features in the native peptide that are important for receptor activation. Although CD expts. yielded equivocal

results, reinforcement of the characteristics of amphiphilicity, helicity, and peptide dipolar effects, using recognized medicinal chemical approaches including introduction of conformational constraints, has resulted in several potent GHRH analogs.

IT **202127-72-8 202127-90-0**

RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)

(systematic structure-activity relationship studies of human growth hormone-releasing hormone hGHRH(1-29)-NH2)

RN 202127-72-8 CAPLUS

CN L-Argininamide, N-methyl-L-tyrosyl-L-alanyl-L-α-aspartyl-L-alanyl-L-isoleucyl-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-α-glutamyl-L-lysyl-L-valyl-L-lysyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-α-aspartyl-L-isoleucyl-L-norleucyl-L-seryl-, (11→14)-lactam (9CI) (CA INDEX NAME)

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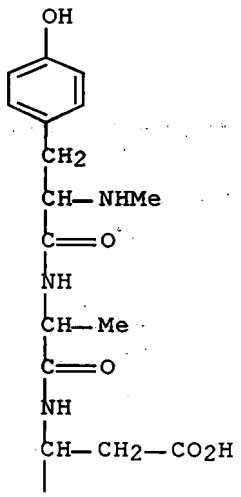

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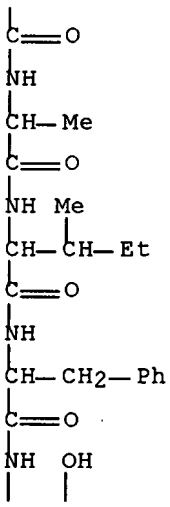

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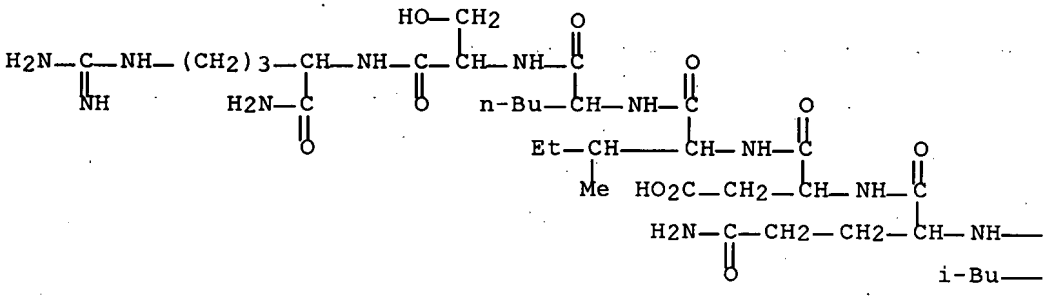

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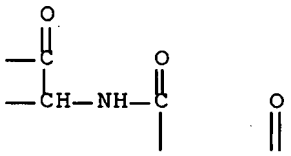

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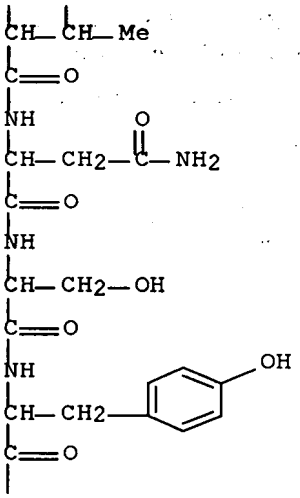

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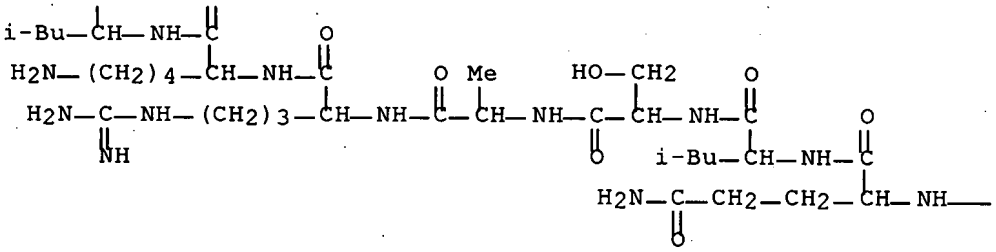

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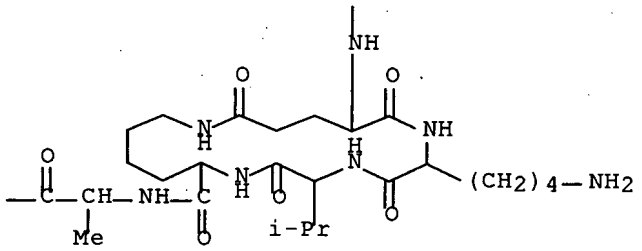

RN 202127-90-0 CAPLUS

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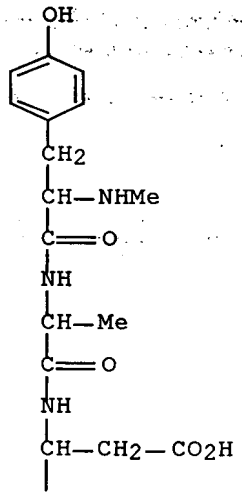

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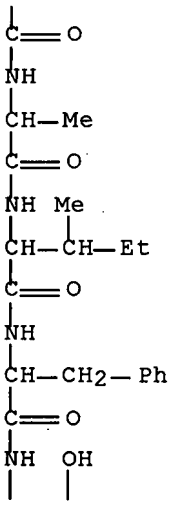

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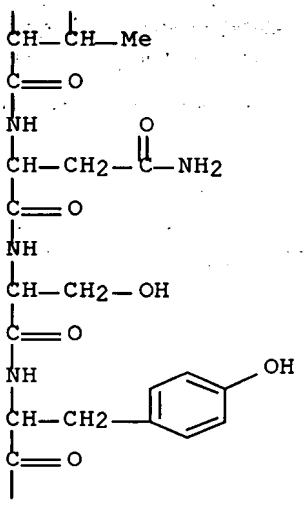

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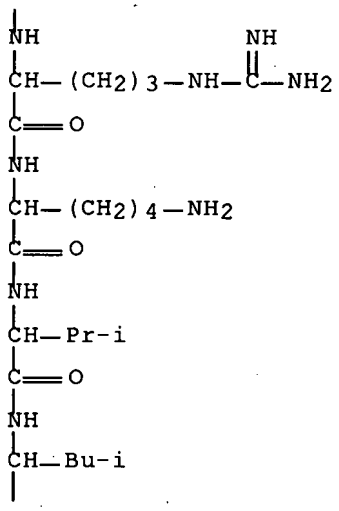

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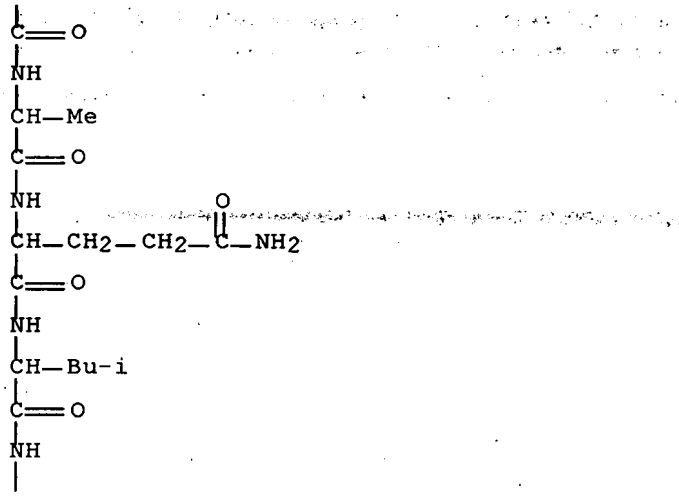

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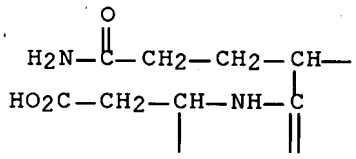

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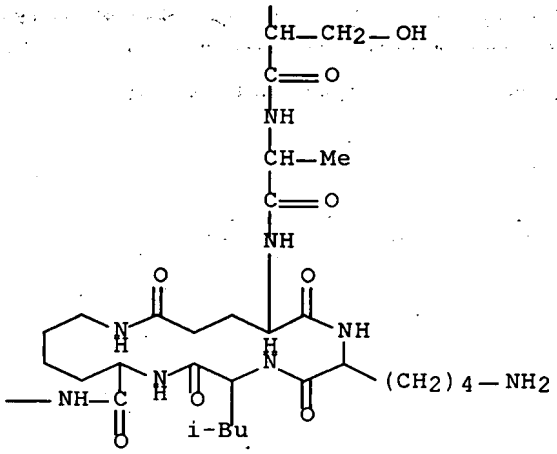

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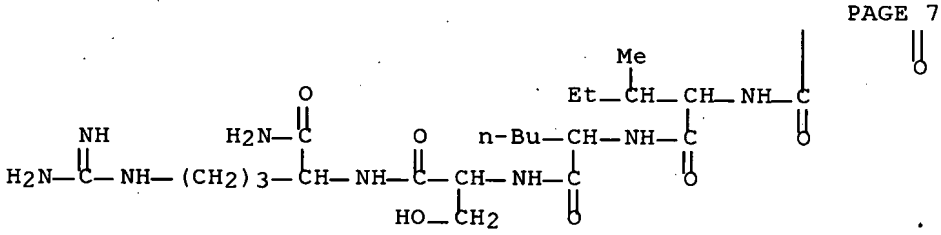


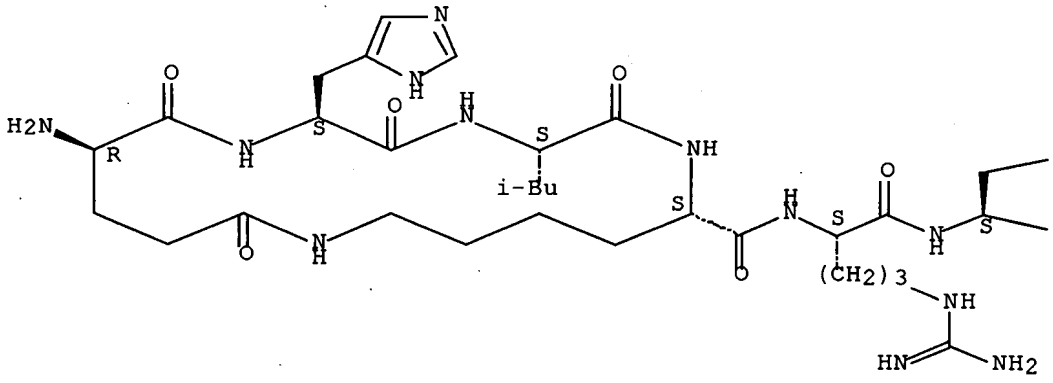
REFERENCE COUNT: 85 THERE ARE 85 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:638464 CAPLUS Full-text
DOCUMENT NUMBER: 127:314402
TITLE: Constrained Corticotropin-Releasing Factor Antagonists with i-(i + 3) Glu-Lys Bridges
AUTHOR(S): Miranda, Antonio; Lahrichi, Sabine L.; Gulyas, Jozsef; Koerber, Steven C.; Craig, Anthony G.; Corrigan, Anne; Rivier, Catherine; Vale, Wylie; Rivier, Jean
CORPORATE SOURCE: Clayton Foundation Laboratories for Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Medicinal Chemistry (1997), 40(22), 3651-3658
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 09 Oct 1997
AB Hypothesis driven and systematic structure-activity relationship (SAR) investigations have resulted in the development of effective central nervous system (CNS) antagonists of corticotropin (ACTH)-releasing factor (CRF) such as α-helical CRF(9-41) and analogs of our assay standard [DPhe12,Nle21,38]hCRF(12-41). On the other hand, equally potent CRF antagonists that block the hypothalamic/pituitary/adrenal (HPA) axis had not been described until recently. Predictive methods, physicochem. measurements (NMR spectrometry and CD spectroscopy), and SAR studies suggest that CRF and its family members (urotensins and sauvagine) assume an α-helical conformation when interacting with CRF receptors. To further test this hypothesis, we have systematically scanned the hCRF(9-41) or hCRF(12-41) sequences with an i-(i + 3) bridge consisting of the Glu-Xaa-Xbb-Lys scaffold which we and others had shown could maintain or enhance α-helical structure. From this series we have identified seven analogs that are either equipotent to, or 3 times more potent than, the assay standard; in addition, as presented earlier, cyclo(30-33)[DPhe12,Nle21,38,Glu30,Lys33]hCRF(12-41) (astressin) is 32 times more potent than the assay standard in blocking ACTH secretion in vitro (rat pituitary cell culture assay). In vivo, astressin is also significantly more potent than earlier antagonists at reducing hypophysial ACTH secretion in intact stressed or adrenalectomized rats. Since the corresponding linear analogs that were tested are significantly less potent, our interpretation of the increased potency of the cyclic analogs is that the introduction of the side chain to side chain bridging element (Glu30---Lys33, and to a lesser extent that of Glu14---Lys17, Glu20---Lys23, Glu23---Lys26, Glu26---Lys29, Glu28---Lys31, Glu29---Lys32, and Glu33---Lys36) induces and stabilizes in the receptor environment a putative α-helical bioactive conformation of the fragment that is not otherwise heavily represented. The effect of the introduction of two favored substitutions [cyclo(20-23) and cyclo(30-33)] yielded the compound with a potency 8 times that of the assay standard but actually 12 times less than expected if the effect of the two cycles had been multiplicative. These results suggest that the pituitary CRF receptor can discriminate between slightly different identifiable conformations, dramatically illustrating the role that secondary and tertiary structures play in modulating biol. signaling through specific protein-ligand interactions.
IT **158068-34-9P 183615-23-8P 197443-72-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PNU (Preparation, unclassified); PRP (Properties); BIOL (Biological study); PREP (Preparation)
(preparation of constrained corticotropin-releasing factor antagonists with i-(i + 3) Glu-Lys lactam bridges)
RN 158068-34-9 CAPLUS
CN Corticotropin-releasing factor (human), 1-de-L-serine-2-de-L-glutamic

acid-3-de-L-glutamic acid-4-de-L-proline-5-de-L-proline-6-de-L-isoleucine-7-de-L-serine-8-de-L-leucine-9-de-L-aspartic acid-10-de-L-leucine-11-de-L-threonine-12-D-glutamic acid-15-L-lysine-21-L-norleucine-38-L-norleucine-, cyclic (12→15)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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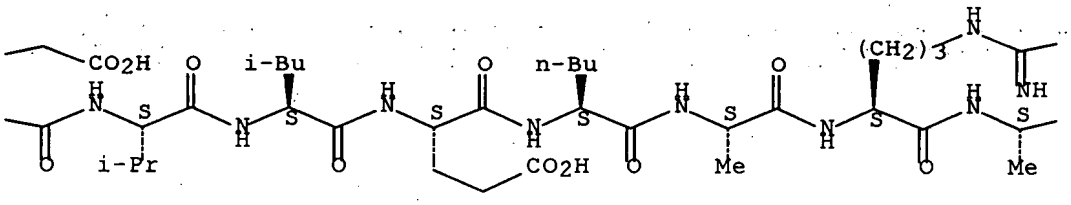

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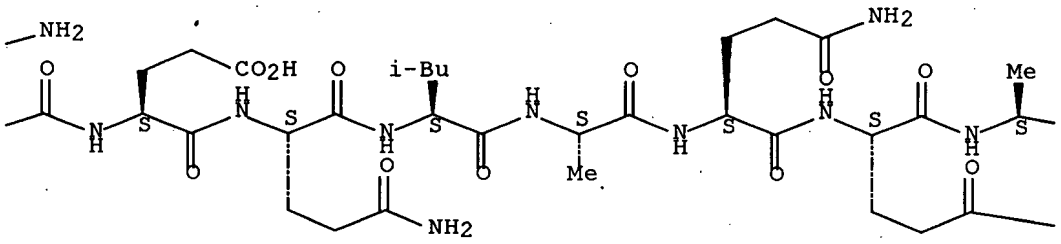

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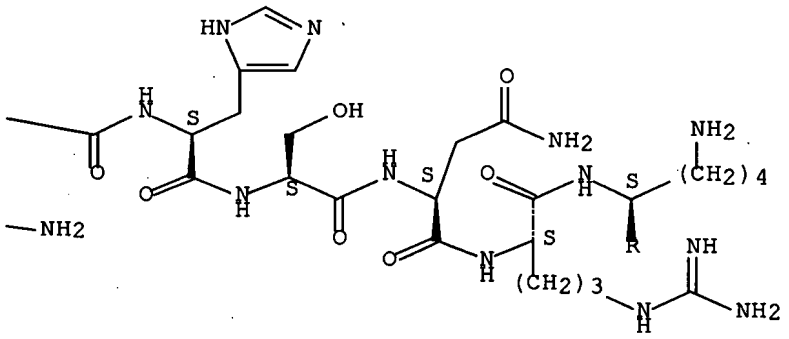

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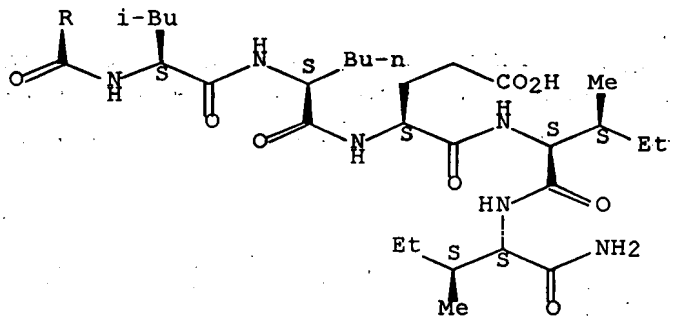

RN 183615-23-8 CAPLUS
CN 12-41-Corticotropin-releasing factor (human), 12-D-phenylalanine-21-L-norleucine-35-L-glutamic acid-38-L-lysine-, cyclic (35→38)-peptide (9CI) (CA INDEX NAME)

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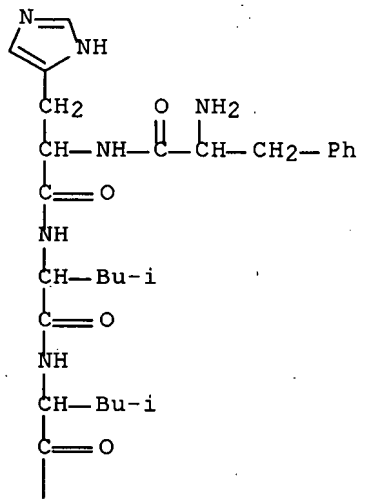

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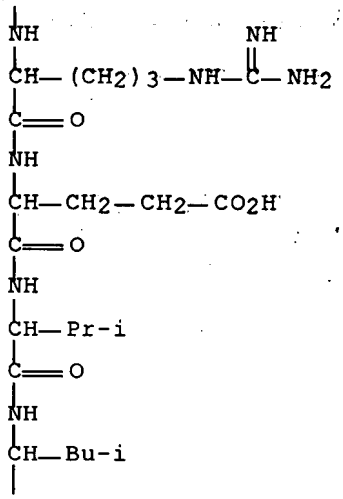

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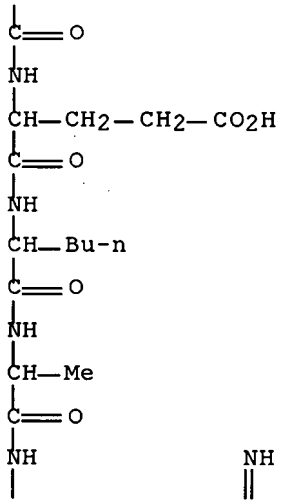

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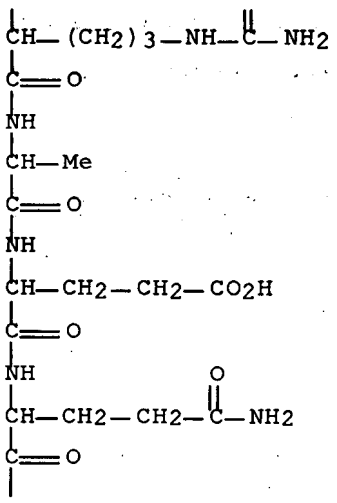

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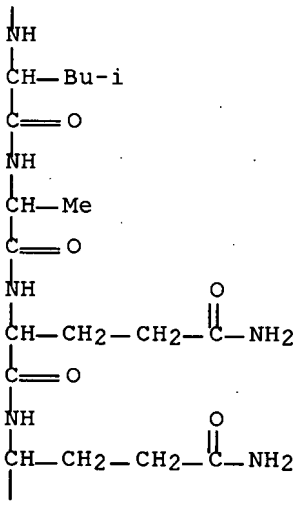

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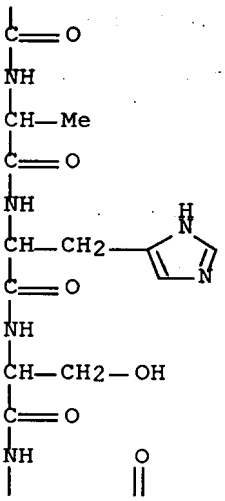

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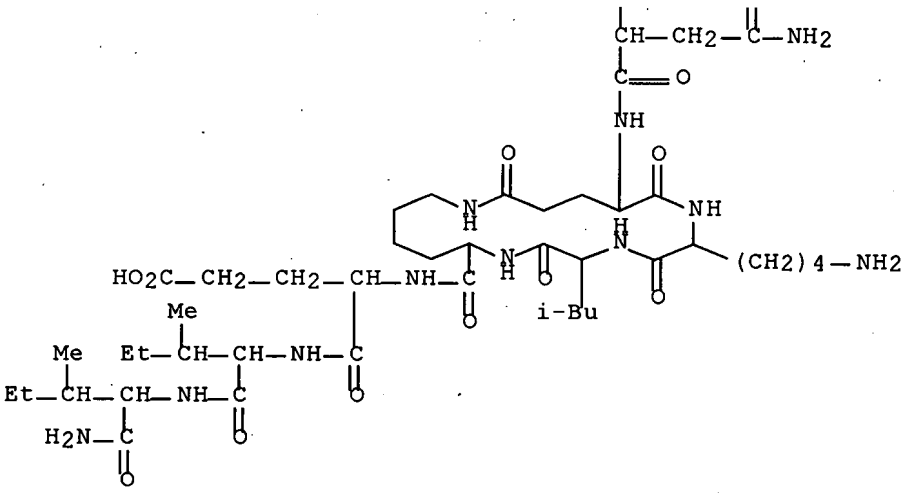
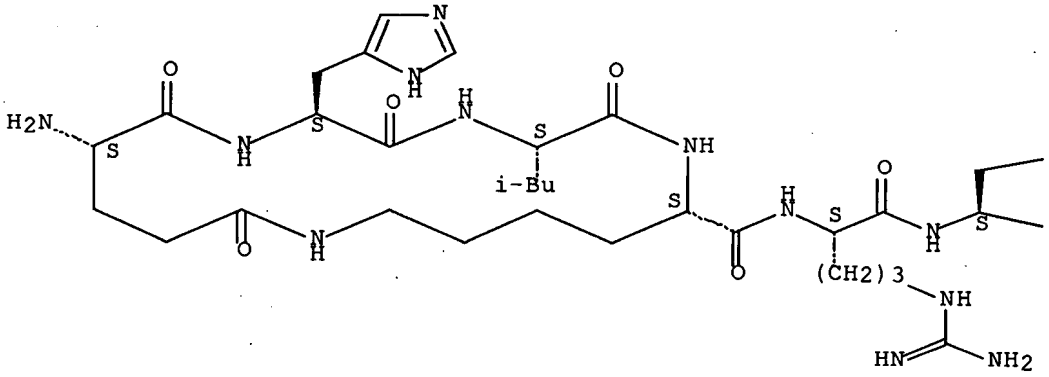


RN 197443-72-4 CAPLUS

CN L-Isoleucinamide, L-α-glutamyl-L-histidyl-L-leucyl-L-lysyl-L-arginyl-L-α-glutamyl-L-valyl-L-leucyl-L-α-glutamyl-L-norleucyl-L-alanyl-L-arginyl-L-alanyl-L-α-glutamyl-L-glutaminyl-L-leucyl-L-alanyl-L-glutaminyl-L-glutaminyl-L-alanyl-L-histidyl-L-seryl-L-asparaginyl-L-arginyl-L-lysyl-L-leucyl-L-norleucyl-L-α-glutamyl-L-isoleucyl-, (1→4)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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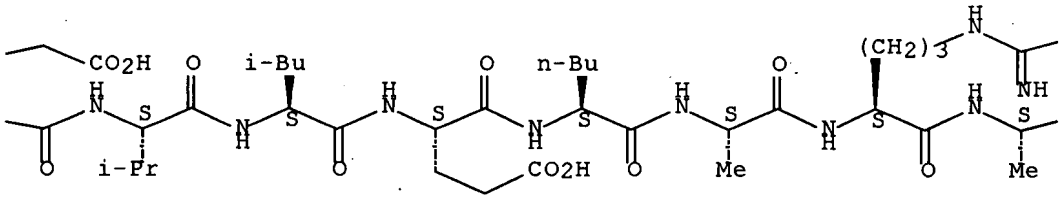

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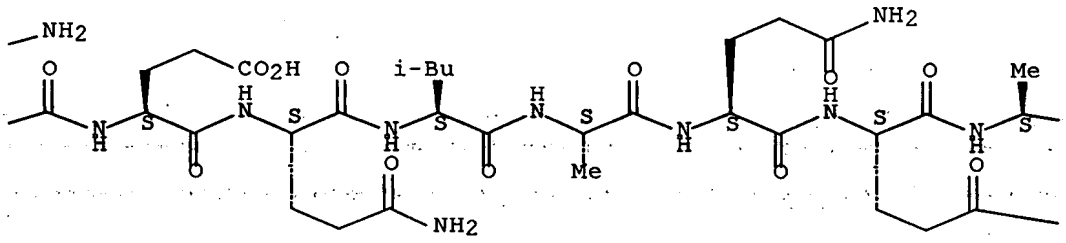

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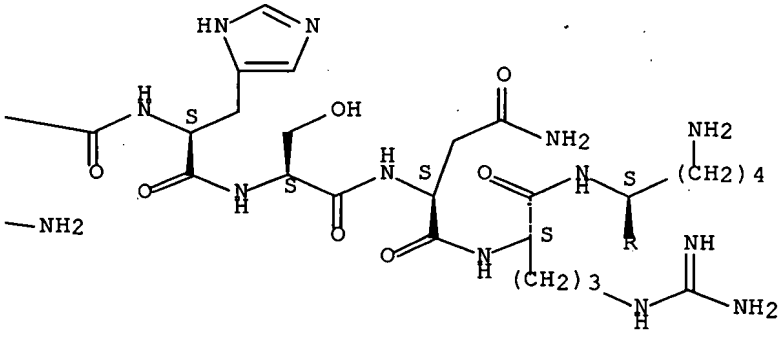
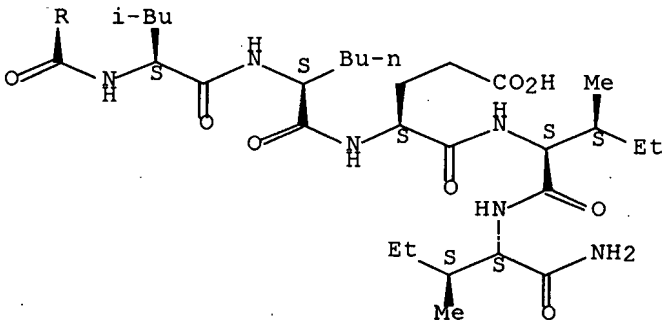




REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L35 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:198118 CAPLUS Full-text
DOCUMENT NUMBER: 126:258432
TITLE: Synthesis and Opioid Activity of Conformationally Constrained Dynorphin A Analogs. 2. Conformational Constraint in the "Address" Sequence
AUTHOR(S): Arttamangkul, Seksiri; Ishmael, Jane E.; Murray, Thomas F.; Grandy, David K.; DeLander, Gary E.; Kieffer, Brigitte L.; Aldrich, Jane V.
CORPORATE SOURCE: College of Pharmacy and Center for Gene Research and Biotechnology, Oregon State University, Corvallis, OR, 97331, USA
SOURCE: Journal of Medicinal Chemistry (1997), 40(8), 1211-1218
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 27 Mar 1997

AB Several cyclic lactam analogs of Dyn A-(1-13)NH2 were prepared to reduce the conformational flexibility in different regions of the native linear peptide. Cyclo[D-Aspi,Dapi+3]Dyn A-(1-13)NH2 (Dap = α,β- diaminopropionic acid) analogs were designed on the basis of mol. modeling using AMBER, which suggested that this constraint may be compatible with an α-helix. The cyclic portion of these constrained analogs spanned from residues 3 to 9, a region proposed by Schwyzer (Biochem. 1986, 25, 4281) to adopt a helical conformation at κ receptor sites. Analogs containing Dab (α,γ-diaminobutyric acid) or Orn in position i + 3 were also synthesized to examine the effects of larger ring size. The cyclic peptides exhibited marked differences in binding affinities for κ, μ, and δ receptors and in opioid activity in the guinea pig ileum (GPI). Cyclo[D-Asp6,Dap9]Dyn A-(1-13)NH2 showed both high κ receptor affinity and potent agonist activity in the GPI, while cyclo[D-Asp3,Dap6]Dyn A-(1-13)NH2 exhibited very weak binding affinity at all opioid receptors as well as very weak opioid activity in the GPI. Cyclo[D-Asp5,Dap8]Dyn A-(1-13)NH2 showed moderate binding affinity for κ receptors and was the most κ selective ligand in this study, but this peptide exhibited very weak agonist activity in the GPI assay. Compared to the corresponding linear peptides, all of the cyclic peptides exhibited decreased μ receptor affinity, while κ receptor affinity was retained or improved. Therefore the corresponding linear peptides were generally μ selective while the cyclic constrained peptides demonstrated slight selectivity for κ vs. μ receptors or were nonselective. Increasing the

ring size by incorporating Dab or Orn in positions 6, 8, or 9 did not significantly affect the binding affinity for the three opioid receptor types nor the opioid activity observed in the GPI. CD spectra of the cyclo[D-Aspi,Dapi+3] derivs. in 80% trifluoroethanol at 25 and 5° suggested differences in the stability of a helical structure when the constraint was incorporated near the N-terminus vs. in the middle of the peptide.

IT **159860-30-7P 188749-30-6P 188749-31-7P**

RL: BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)

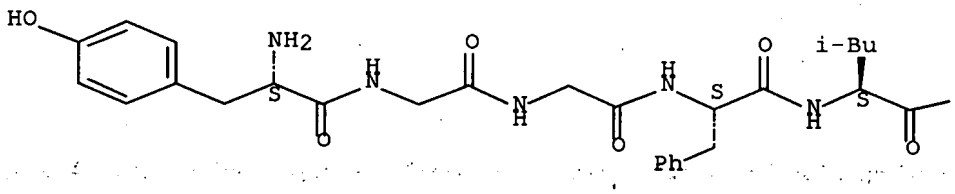
(synthesis and opioid activity of conformationally constrained dynorphin a analogs)

RN 159860-30-7 CAPLUS

CN 1-13-Dynorphin A (swine), 6-D-aspartic acid-9-(3-amino-L-alanine)-13-L-lysinamide-, cyclic (6→9)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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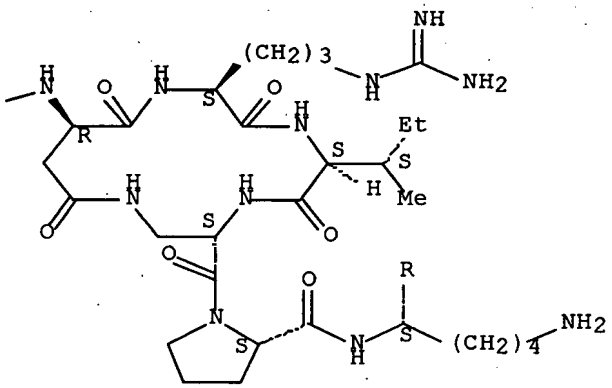

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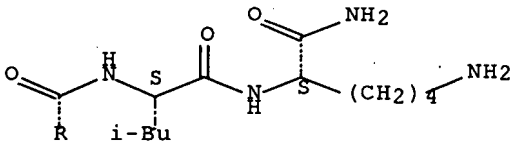
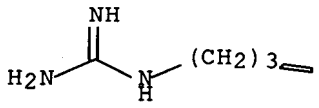


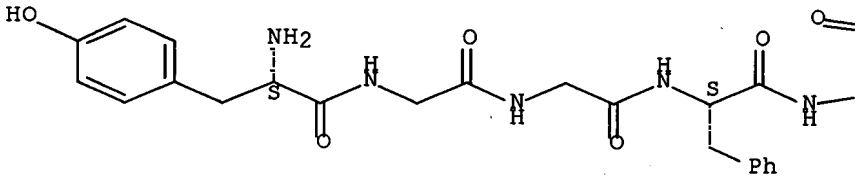
RN 188749-30-6 CAPLUS

CN 1-13-Dynorphin A (swine), 6-D-aspartic acid-9-[(2S)-2,4-diaminobutanoic acid]-13-L-lysinamide-, (6→9)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





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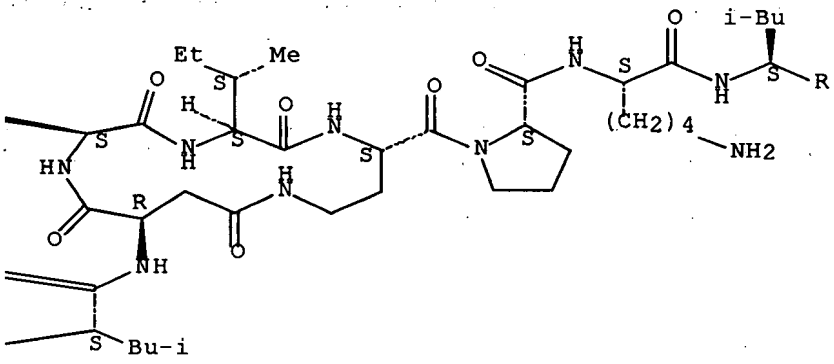

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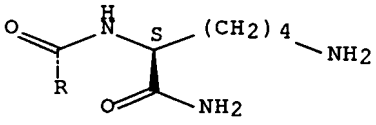
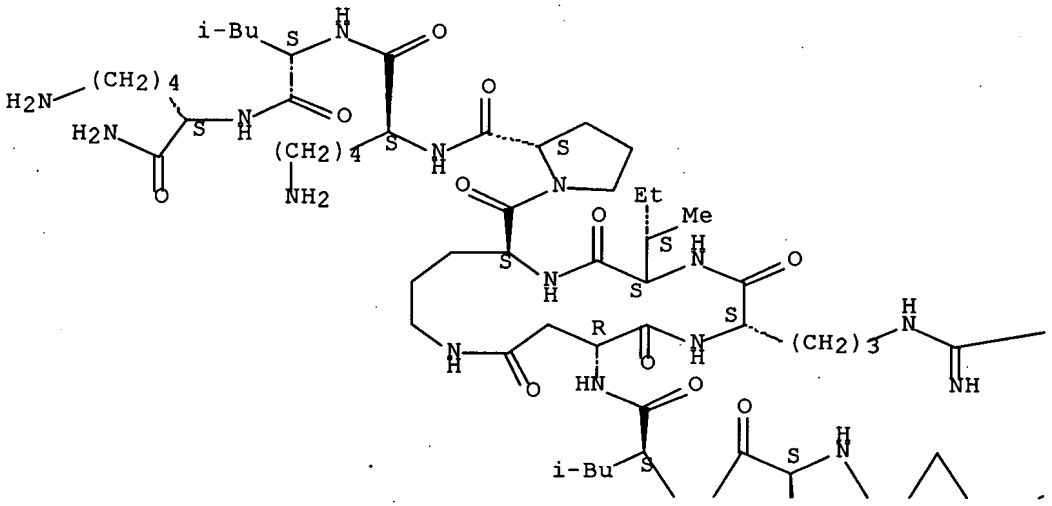


RN 188749-31-7 CAPLUS

CN 1-13-Dynorphin A (swine), 6-D-aspartic acid-9-L-ornithine-13-L-lysinamide-, (6→9)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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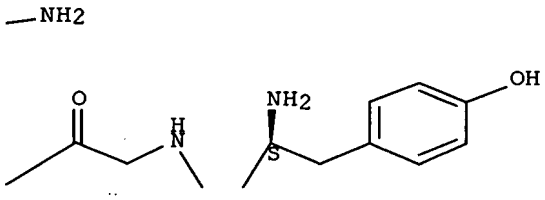

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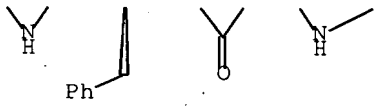

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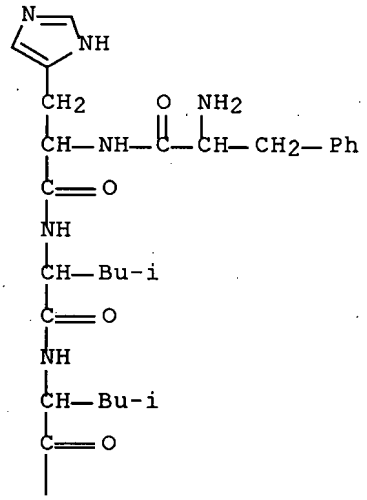
L35 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:714345 CAPLUS Full-text
DOCUMENT NUMBER: 126:55001
TITLE: Structure activity relationships (SAR) of corticotropin releasing factor
AUTHOR(S): Rivier, Jean; Rivier, Catherine; Sutton, Steve; Miranda, Antonio; Koerber, Steven C.; Gulyas, Jozsef; Lahrichi, Sabine L.; Corrigan, Anne; Craig, A. Grey; Vale, Wylie
CORPORATE SOURCE: Clayton Foundation Laboratories Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Peptides: Biology and Chemistry, Proceedings of the Chinese Peptide Symposium, 3rd, Beijing, June 13-17, 1994 (1995), Meeting Date 1994, 195-198. Editor(s): Lu, Gui-Shen; Tam, James P.; Du, Yu-Cang. ESCOM: Leiden, Neth.
CODEN: 63QWA5
DOCUMENT TYPE: Conference
LANGUAGE: English
ED Entered STN: 05 Dec 1996
AB To test the hypothesis that CRF assumes an α-helical conformation on binding to its pituitary receptor, the authors systematically scanned the entire length of the CRF sequence with an i(i+3) Glu/Lys lactam bridge. Tests of 13 peptides for CRF antagonist activity showed that introduction of the lactam bridge may affect potency. Deletion at the N- and C-termini yielded agonist analogs with high affinity for CRF-binding protein but no affinity for the CRF receptor.
IT **183615-23-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structure-activity relations of CRF peptide analogs)
RN 183615-23-8 CAPLUS
CN 12-41-Corticotropin-releasing factor (human), 12-D-phenylalanine-21-L-norleucine-35-L-glutamic acid-38-L-lysine-, cyclic (35→38)-peptide (9CI) (CA INDEX NAME)

PAGE 1-A



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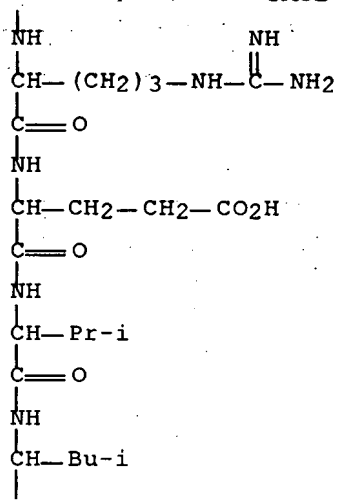

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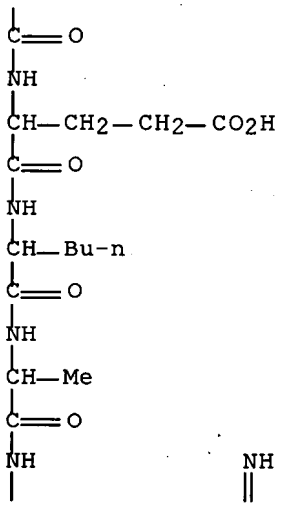

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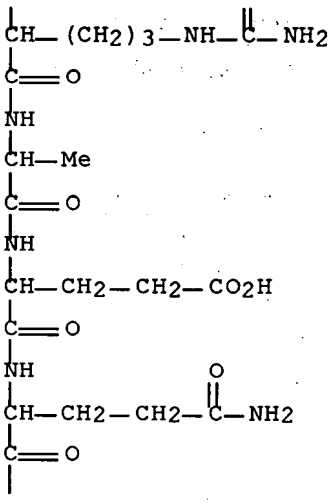

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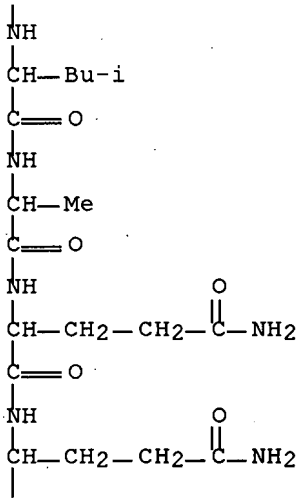

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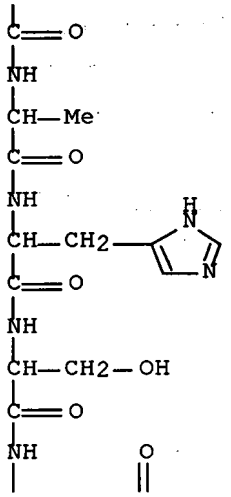

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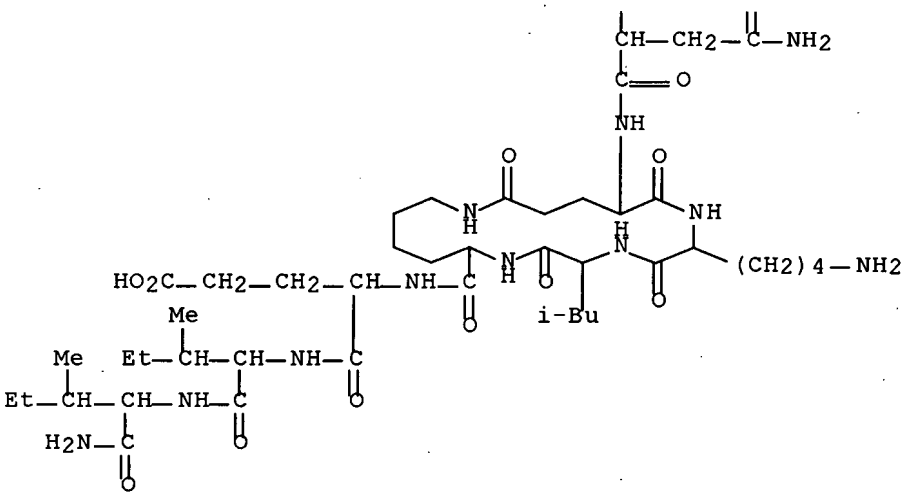
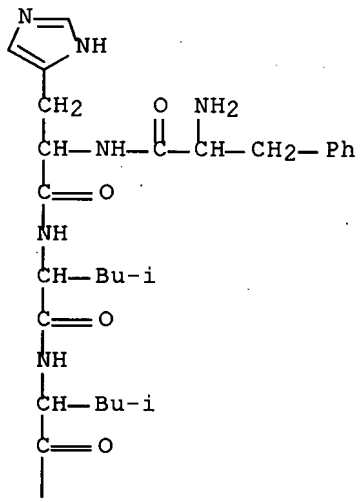


L35 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:639304 CAPLUS Full-text
DOCUMENT NUMBER: 126:1285
TITLE: SAR of corticotropin releasing factor in relation to its pituitary receptor and binding protein
AUTHOR(S): Rivier, J.; Rivier, C.; Sutton, S.; Miranda, A.; Koerber, S. C.; Gulyas, J.; Lahrichi, S. L.; Corrigan, A.; Craig, A. G.; Vale, W.
CORPORATE SOURCE: Clayton Foundation Laboratories Peptide Biology, Salk Institute, La Jolla, CA, 92037, USA
SOURCE: Peptides 1994, Proceedings of the European Peptide Symposium, 23rd, Braga, Port., Sept. 4-10, 1994 (1995) , Meeting Date 1994, 103-104. Editor(s): Maia, Hernani L. S. ESCOM: Leiden, Neth.
CODEN: 63MBAO
DOCUMENT TYPE: Conference
LANGUAGE: English
ED Entered STN: 30 Oct 1996

AB CRF has been postulated to assume an α-helical conformation upon binding to its pituitary receptor on the basis of Cα-Me substitutions of some amino acids in the sequence that led to more potent analogs and CD spectra, which showed significant α-helical content. The authors have exploited this hypothesis in synthesizing an i-(i+3) bridge scan (i.e., Glu-X-X-Lys) of the CRF sequence. Early results on that series and SAR of CRFBP and some selected ligands are presented.

IT **183615-23-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(SAR of ACTH releasing factor in relation to pituitary receptor and binding protein)
RN 183615-23-8 CAPLUS
CN 12-41-Corticotropin-releasing factor (human), 12-D-phenylalanine-21-L-norleucine-35-L-glutamic acid-38-L-lysine-, cyclic (35→38)-peptide (9CI) (CA INDEX NAME)

PAGE 1-A



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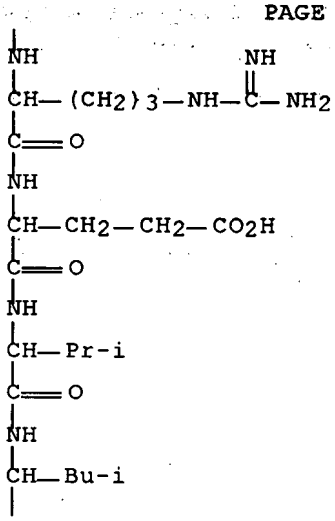

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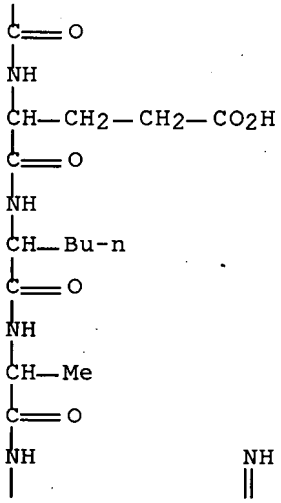

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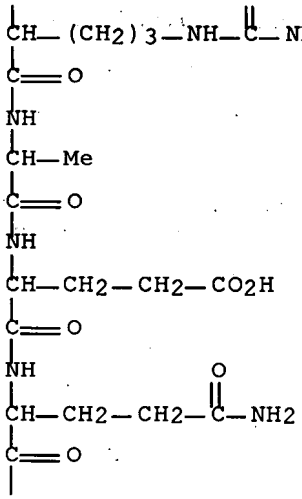

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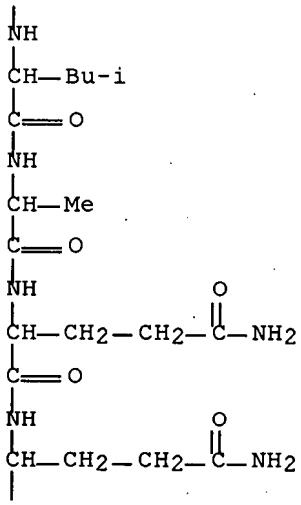

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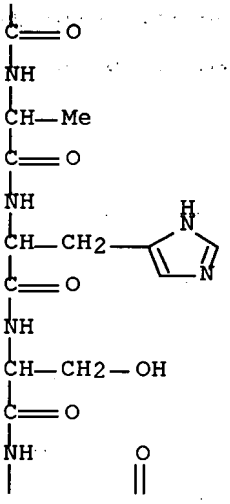

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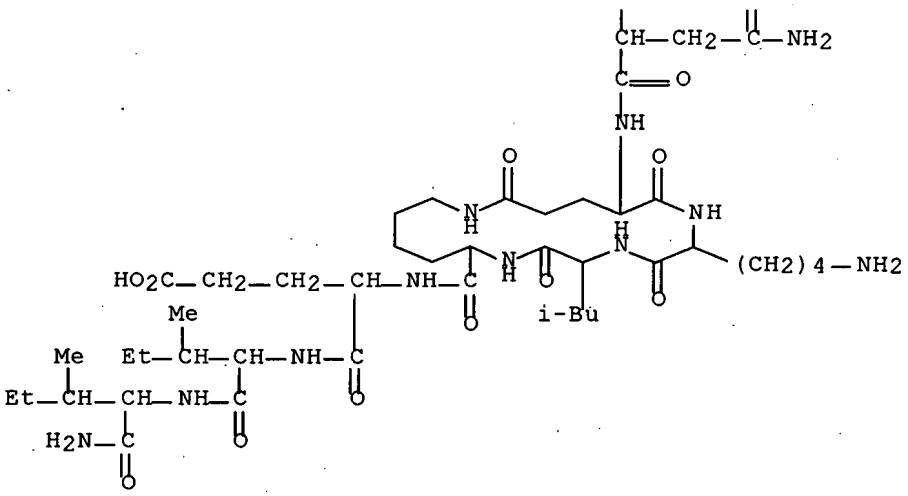
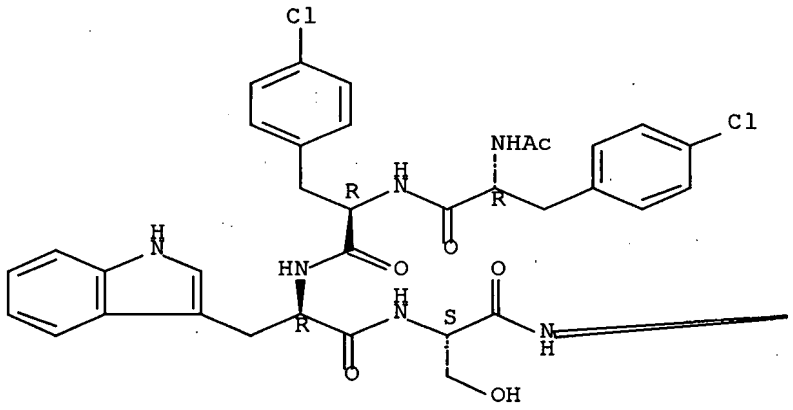


L35 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:679265 CAPLUS Full-text
DOCUMENT NUMBER: 123:75085
TITLE: NMR studies on the structure of some cyclic and linear antagonists of luteinizing hormone-release hormone (LHRH)
AUTHOR(S): Reddy, D. V.; Jagannadh, B.; Dutta, S.; Kunwar, A. C.
CORPORATE SOURCE: Indian Inst. Chem. Technology, Hyderabad, 500 007, India
SOURCE: International Journal of Peptide & Protein Research (1995), 46(1), 9-17
CODEN: IJPPC3; ISSN: 0367-8377
PUBLISHER: Munksgaard
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 15 Jul 1995
AB The structure of cyclic antagonists of LH-releasing hormone (LHRH), Ac-D-Phe(p-Cl)1-D-Phe(p-Cl)2-D-Trp3-Ser4-c(Asp5-D-Arg6-Leu7-Lys8)-Pro9-D- Ala10-NH2 (I), Ac-D-Phe(p-Cl)1-D-Phe(p-Cl)2-D-Trp3-Ser4-c(Glu5-D-Arg6-Leu7- Lys8)-Pro9-D-Ala10-NH2 (II) and their linear analogs, Ac-D-Phe(p-Cl)1-D- Phe(p-Cl)2-D-Trp3-Ser4-Asp5-D-Arg6-Leu7-Lys8-Pro9-D-Ala10-NH2 (III) and Ac-D-Phe(p-Cl)1-D-Phe(p-Cl)2-D-Trp3-Ser4-Glu5-D-Arg6-Leu7-Lys8-Pro9-D- Ala10-NH2 (IV), have been studied by NMR spectroscopy. The cyclic peptides I and II are more potent antagonists than the corresponding linear peptides in an in vivo assay. All the peptides show propensity of an unusual type II' β-turn involving residues 3-6. Cyclic analogs also show some addnl. structure around residues 7 and 8 which is absent in the linear peptides. This addnl. structure in the cyclic peptides may be due to a minor conformation with a β-turn between residues 5 and 8.
IT **121279-17-2 121279-19-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(NMR studies on the structure of some cyclic and linear antagonists of LH-RH)
RN 121279-17-2 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-

, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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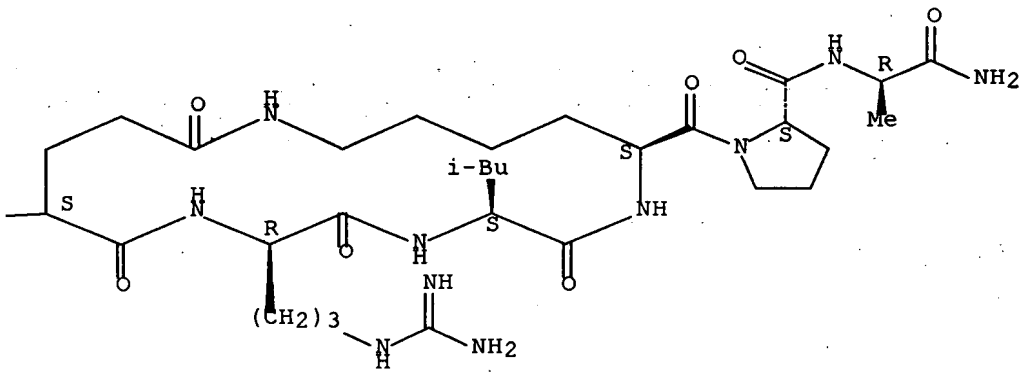
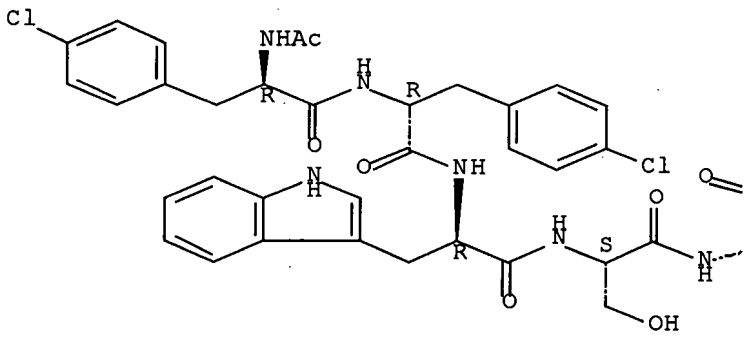


RN 121279-19-4 CAPLUS

CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-aspartyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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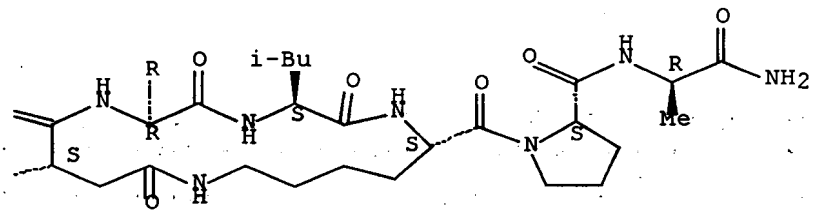

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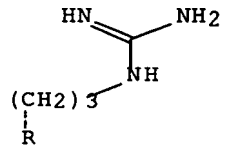


L35 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:259368 CAPLUS Full-text
DOCUMENT NUMBER: 122:23989
TITLE: Synthesis and opioid activity of conformationally constrained dynorphin A analogs
AUTHOR(S): Arttamangkul, S.; Murray, T. F.; DeLander, G. E.; Aldrich, J. V.
CORPORATE SOURCE: Coll. Pharmacy, Oregon State Univ., Corvallis, OR, 97331, USA
SOURCE: Regulatory Peptides (1994), 54(1), 13-14
CODEN: REPPDY; ISSN: 0167-0115
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 22 Dec 1994

AB Cyclic analogs of dynorphin A-(1-13) amide (Dyn A-(1-13)NH2) were synthesized and their opioid receptor affinity and opioid activity determined Cyclic peptides constrained in both the "message" and "address" regions of Dyn A-(1-13)NH2 were prepared to investigate possible biol. conformations of different regions of the peptides. The design of the constraint was based upon Schwyzer's proposal that Dyn A-(1-13) adopts an α-helix when it binds to κ opioid receptors in the lipid membrane. Mol. modeling with AMBER suggested that a four atom bridge between the α carbons of residues i (D-configuration) and i+3 (L-configuration) may be compatible with a helical structure. Therefore the authors synthesized a series of cyclo[D-Aspi,Dapi+3]Dyn A-(1-13)NH2 analogs (Dap = α,β-diaminopropionic acid) with the lactam bridge between noncrit. residues 2 and 5, 3 and 6, 5 and 8, or 6 and 9. Of these cyclic peptides, the [2,5] cyclic analog exhibited the highest opioid receptor affinity and opioid activity.

IT **159860-30-7**

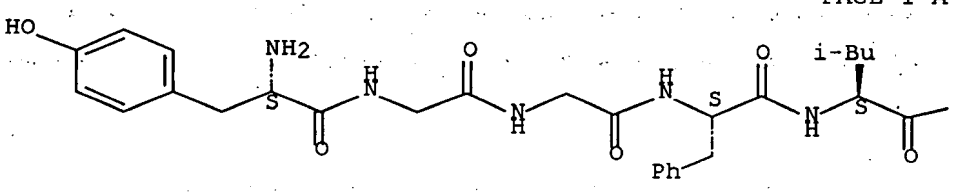
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(dynorphin A analog opioid activities in relation to conformation)

RN 159860-30-7 CAPLUS

CN 1-13-Dynorphin A (swine), 6-D-aspartic acid-9-(3-amino-L-alanine)-13-L-lysinamide-, cyclic (6→9)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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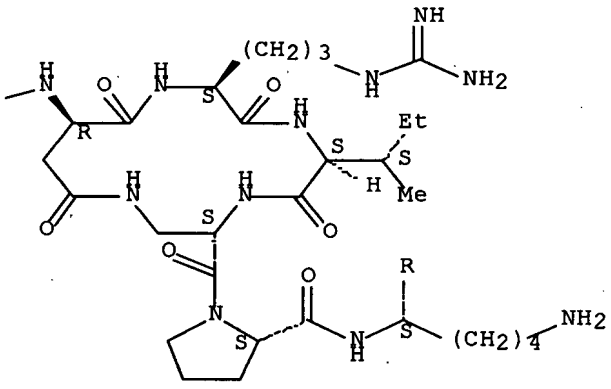
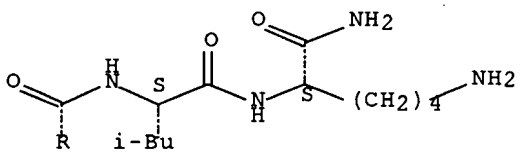
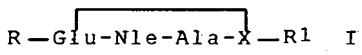




L35 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:605968 CAPLUS Full-text
DOCUMENT NUMBER: 121:205968
TITLE: Conformationally Restricted Competitive Antagonists of Human/Rat Corticotropin-Releasing Factor
AUTHOR(S): Miranda, Antonio; Koerber, Steven C.; Gulyas, Jozsef; Lahrichi, Sabine L.; Craig, A. Grey; Corrigan, Anne; Hagler, Arnold; Rivier, Catherine; Vale, Wylie; Rivier, Jean
CORPORATE SOURCE: Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SOURCE: Journal of Medicinal Chemistry (1994), 37(10), 1450-9
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 29 Oct 1994
GI



AB The postulated α-helical conformation of ACTH releasing factor (CRF) assumed upon binding to its pituitary receptor was exploited in the design of a limited series of cyclic analogs. The effects of side chain deletion and as well as of changes in chirality were considered, with the rationale that side chains necessary for binding could also be replaced by side chain bridges. In particular, computer modeling was used to predict likely side chain bridging opportunities and the effects of such replacements was evaluated by correlating biol. results with those derived from CD spectroscopy. Thus, 38 monocyclic peptide amides, competitive antagonists of human/rat CRF, were prepared using solid-phase methodol. on MBHA resins. After purification by preparative reversed-phase (RP) HPLC, the peptides were analyzed by RP-HPLC and capillary zone electrophoresis and characterized by mass spectrometry and amino acid anal. CRF antagonists were tested for their ability to interfere with CRF-induced release of ACTH by rat anterior pituitary cells. In most cases, one of the bridgehead positions was located at a position where substitution by a D-residue was tolerated (i.e., positions 12 and 20). It become clear that careful optimization of bridge length and chirality is critical This is best exemplified by the fact that out of the 38 cyclic analogs prepared and tested, only two, (I; R = H-D-Phe12-His-Leu-Leu-Arg-Glu-Val-Leu, X = Lys-Orn, R1 = Ala-Glu-Gln-Leu-Ala-Gln-Gln30-Ala-His-Ser-Asn-Arg-Lys-Leu- Nle-Glu-Ile40-Ile-NH2) were more potent (3 and 2 times, resp.) than the parent compd R-Glu20-Nle-Ala-Arg-R1. Six analogs belonging to two different families were half as potent as the standard, 18 had 2-20% of the

potency of the standard, and the others were significantly less potent. CD results of all analogs in 50% 2,2,2-trifluoroethanol suggest that while helicity may be an important factor for CRF analog recognition, little correlation is found between % helicity as determined by spectral deconvolution and biol. activity in vitro.

IT **158068-34-9P**

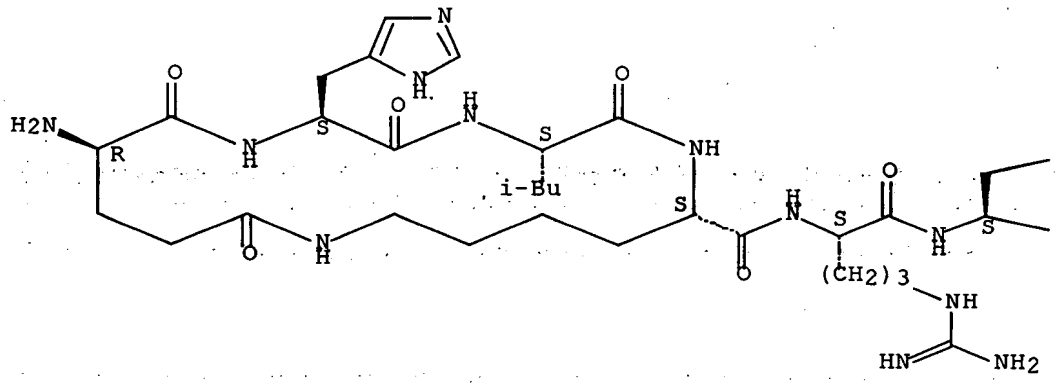
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation, helical conformation, and ACTH-releasing factor antagonistic activity of)

RN 158068-34-9 CAPLUS

CN Corticotropin-releasing factor (human), 1-de-L-serine-2-de-L-glutamic acid-3-de-L-glutamic acid-4-de-L-proline-5-de-L-proline-6-de-L-isoleucine-7-de-L-serine-8-de-L-leucine-9-de-L-aspartic acid-10-de-L-leucine-11-de-L-threonine-12-D-glutamic acid-15-L-lysine-21-L-norleucine-38-L-norleucine-, cyclic (12→15)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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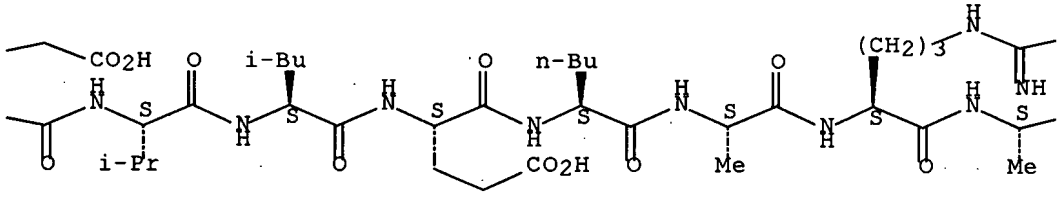

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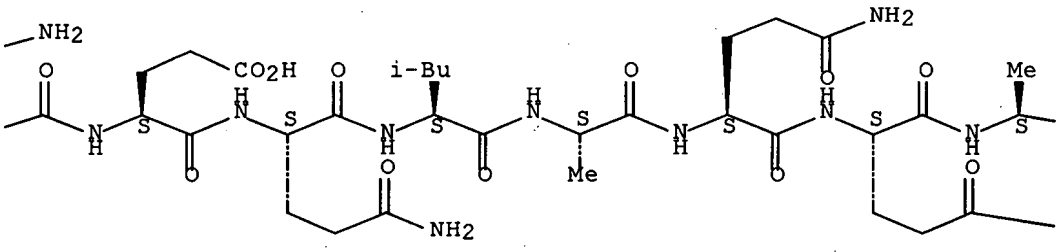

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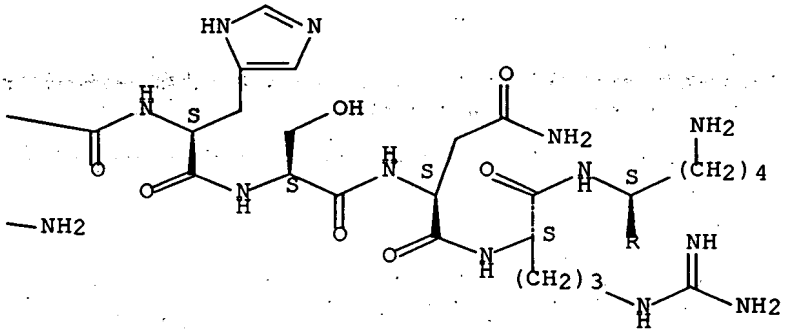

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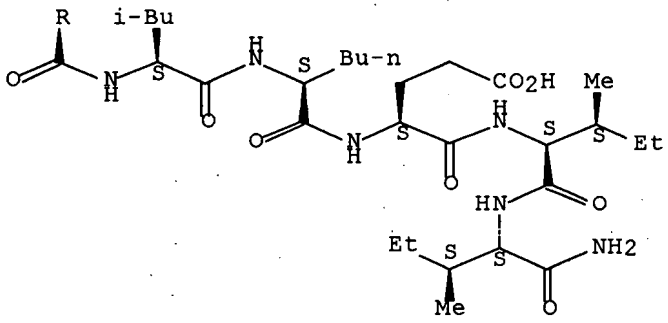


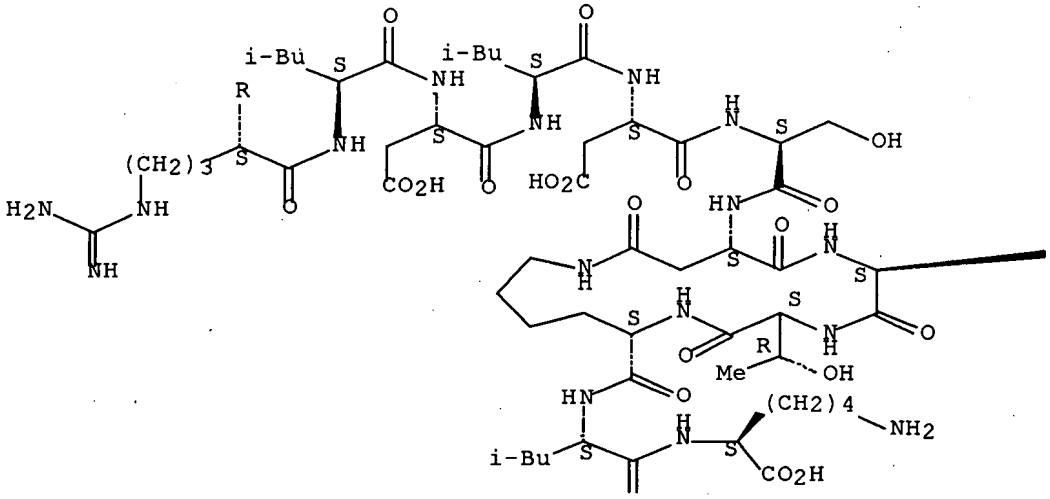
L35 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:317931 CAPLUS Full-text
DOCUMENT NUMBER: 120:317931
TITLE: NMR and circular dichroic studies of the solution structure of conformationally constrained antigenic

peptides

AUTHOR(S): Precheur, Benedicte; Bossus, Marc; Gras-Masse, Helene; Quiniou, Eric; Tartar, Andre; Craescu, Constantin T.
CORPORATE SOURCE: Inst. Curie-Biol., Orsay, F-91405, Fr.
SOURCE: European Journal of Biochemistry (1994), 220(2), 415-25
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 25 Jun 1994
AB Circular dichroic and NMR spectroscopies were used to evaluate the conformational properties in solution of a series of 20-amino-acid peptides derived from the primary structure of an antigen from Echinococcus granulosus. The linear peptide corresponding to the sequence 93-112 in the antigen was found to populate in a significant proportion the α-helix conformational state. In the presence of 2,2,2-trifluoroethanol, a cosolvent known to stabilize peptide secondary structure, the helical population, estimated from circular dichroic spectra, increases up to 60-70%. Two-dimensional NMR studies under these conditions showed that the segment K96-K108 meets all the criteria of an α-helix at 281 K and 298 K. Three different variants were synthesized with the same or similar primary structure but containing a lactam-bridged (>) side chain: D107>K110, D97>K100 and K94>E98. Generally, the observed helical content in these variants was lower than in the parent mol. and the stability of the helical conformation decreased in the order D107, K110, K94, E98, D97, K100. Anal. of chemical shift and nuclear Overhauser enhancement data suggested that the lactam rings induce significant distortions of the local features of helix secondary structure. The possible factors of helix destabilization induced by lactam bridges, observed in the studied peptides are discussed in relation to the stabilizing effect of ion pairs in model compds.
IT **155518-45-9P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(preparation and helical conformation of)
RN 155518-45-9 CAPLUS
CN L-Lysine, L-alanyl-L-lysyl-L-threonyl-L-lysyl-L-leucyl-L-α-glutamyl-L-α-glutamyl-L-valyl-L-arginyl-L-leucyl-L-α-aspartyl-L-leucyl-L-α-aspartyl-L-seryl-L-α-aspartyl-L-lysyl-L-threonyl-L-lysyl-L-leucyl-, cyclic (15→18)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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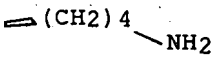

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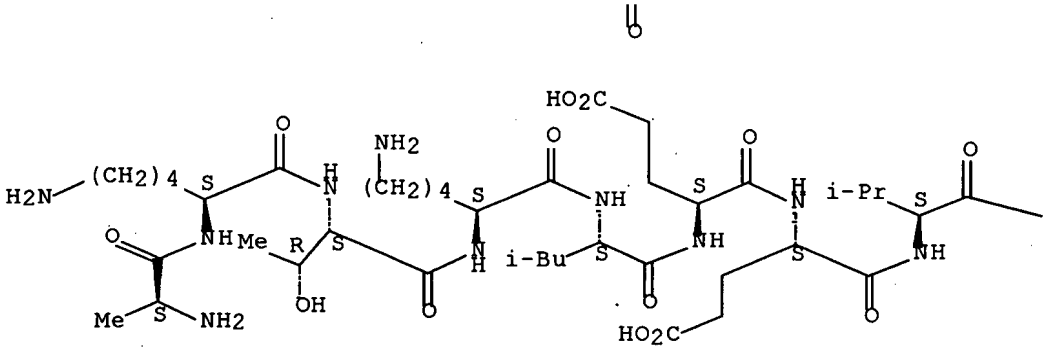
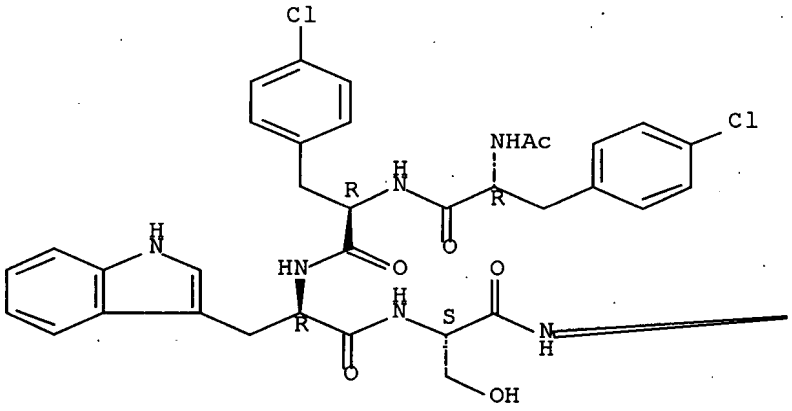


L35 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1993:574311 CAPLUS Full-text
DOCUMENT NUMBER: 119:174311
TITLE: Antagonists of luteinizing hormone-releasing hormone (LHRH). Progress towards non-peptide leads
AUTHOR(S): Dutta, A. S.; Gormley, J. J.; Woodburn, J. R.; Paul, P. K. C.; Osguthorpe, D. J.; Campbell, M. M.
CORPORATE SOURCE: ICI Pharm., Macclesfield/Cheshire, SK10 4TG, UK
SOURCE: Bioorganic & Medicinal Chemistry Letters (1993), 3(5), 943-8
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 30 Oct 1993
AB In an attempt to generate information leading to non-peptide antagonists of LHRH, conformationally restricted analogs of LHRH antagonists have been studied. The design, mol. modeling studies, and biol. activities of several analogs including a bicyclic antagonist c[D-Phe(p-Cl)-D-Phe(p-Cl)- D-Trp-Ser-Glu-D-Arg-Leu-Lys-Pro-D-MeAla], obtained by forming amide bonds between N- and C-terminal ends and between the side chains of Glu and Lys residues, are reported here.
IT **121279-17-2 121279-19-4 121279-28-5**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(LH-RH antagonistic activity of, structure in relation to)
RN 121279-17-2 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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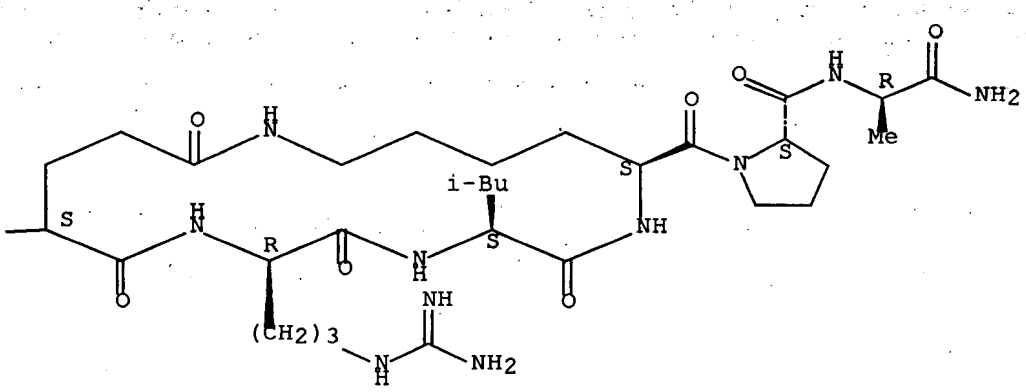
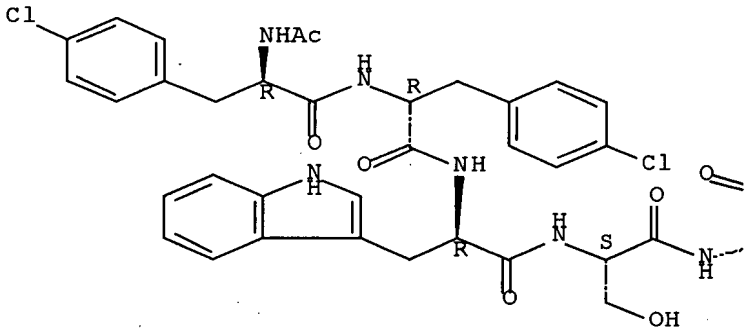


RN 121279-19-4 CAPLUS

CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-aspartyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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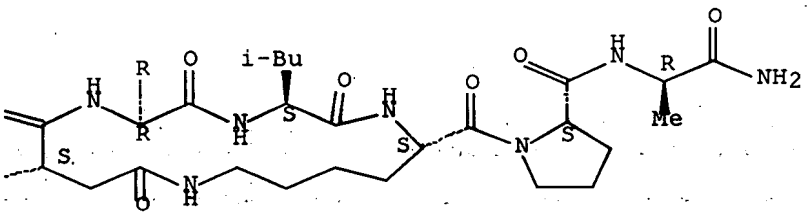

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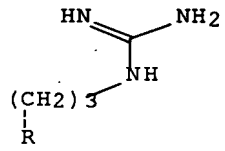
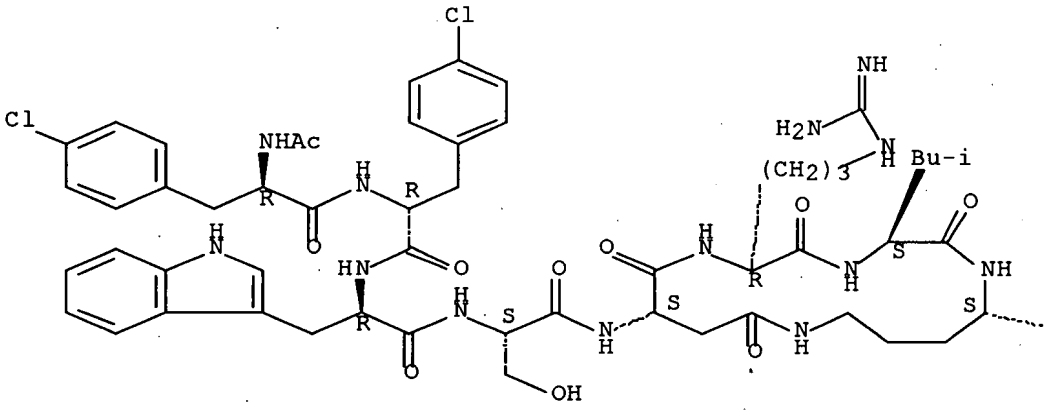


RN 121279-28-5 CAPLUS

CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-aspartyl-D-arginyl-L-leucyl-L-ornithyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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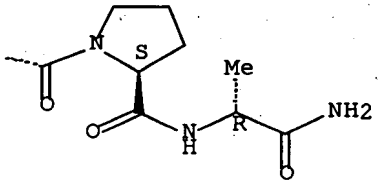


L35 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1990:91921 CAPLUS Full-text
DOCUMENT NUMBER: 112:91921
TITLE: A novel β-turn location in an LH-RH antagonist: a combined conformational search and molecular dynamics study
AUTHOR(S): Paul, P. K. C.; Dauber-Osguthorpe, P.; Campbell, M. M.; Osguthorpe, D. J.
CORPORATE SOURCE: Sch. Chem., Univ. Bath, BA2 7AY, UK
SOURCE: Biochemical and Biophysical Research Communications (1989), 165(3), 1051-8
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 18 Mar 1990
AB A 50 pico-second mol. dynamics simulation on a cyclic LH-RH antagonist analog Ac-D-Phe1-D-Phe2-D-Trp3-Ser4 cyclic (Glu5-D-Arg6-Leu-Lys8)-Pro9-D- Ala10-NH (where the cyclization is via an amide linkage between the Glu5 and Lys6 side

chains) reveals some hitherto unseen conformational features. The LH-RH analog adopted a near β-sheet type of conformation with the reversal in the chain being brought about by a D-Trp3-Ser4-Glu5-D-Arg6 β turn. The N- and C-terminal ends of the peptide come close together and interact through a network of H bonds. Addnl. H bonds expected of a sheet type of conformation stabilize the lowest energy min. A conformational search of all possible cyclic structures of a model system c(Glu-D-Ala-Ala-Lys) which was used to determine the starting structure for the simulation studies of the cyclic LH-RH antagonist analog is also high-lighted. The influence of the cyclic part on the conformation of this LH-RH analog is discussed.

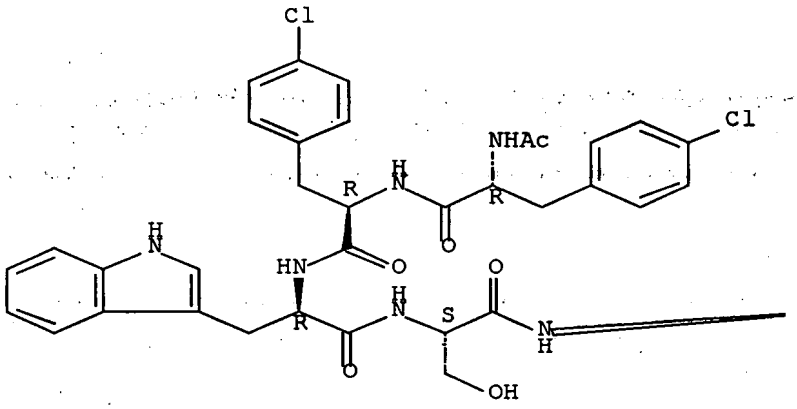
IT **121279-17-2**
RL: PRP (Properties)
(conformation of)

RN 121279-17-2 CAPLUS

CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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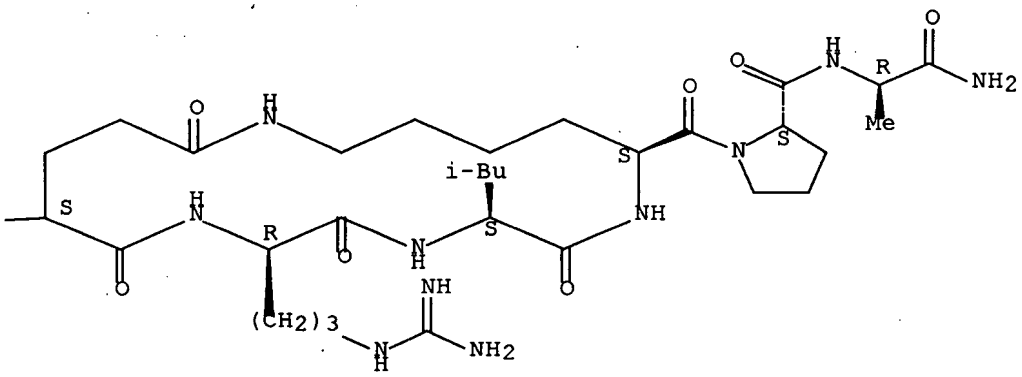
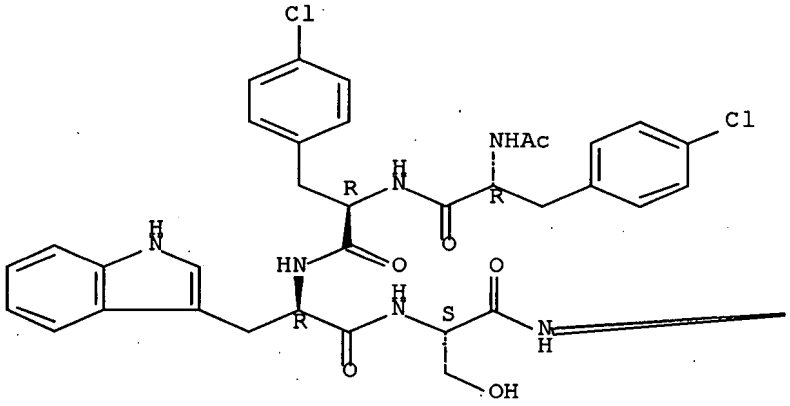


L35 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1989:433762 CAPLUS Full-text
DOCUMENT NUMBER: 111:33762
TITLE: Conformationally restrained cyclic peptides as antagonists of luteinizing hormone-releasing hormone
AUTHOR(S): Dutta, Anand S.; Gormley, James J.; McLachlan, Peter F.; Woodburn, James R.
CORPORATE SOURCE: ICI Pharm., Macclesfield/Cheshire, SK10 4TG, UK
SOURCE: Biochemical and Biophysical Research Communications (1989), 159(3), 1114-20
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
ED Entered STN: 05 Aug 1989
GI For diagram(s), see printed CA Issue.
AB Using min. energy calcns. and mol. dynamics techniques the preferred conformational states of LH-RH and its analogs have been reported to involve a modified β-bend between residues 5 to 8. Based on some of these models cyclic peptide analogs of LH-RH antagonists were synthesized by solid-phase peptide synthesis methodol. The analogs were tested for their ability to inhibit ovulation in normal cycling rats. Some analogs were also tested in receptor binding and in vitro LH release assays. The most potent analog I had an ED50 value of 91.9 μg/kg in the inhibition of ovulation test. The corresponding linear peptide was about 3 times less potent. Analogs with smaller or larger ring sizes or with modifications within the ring were also prepared but these were either less potent or inactive, up to a dose of 1000 μg/kg, in inhibiting ovulation in normal cycling rats.
IT **121279-17-2 121279-19-4 121279-26-3**
121279-28-5 121279-29-6 121279-30-9
RL: BIOL (Biological study)
(ovulation inhibition by, as LH-RH analog, structure in relation to)
RN 121279-17-2 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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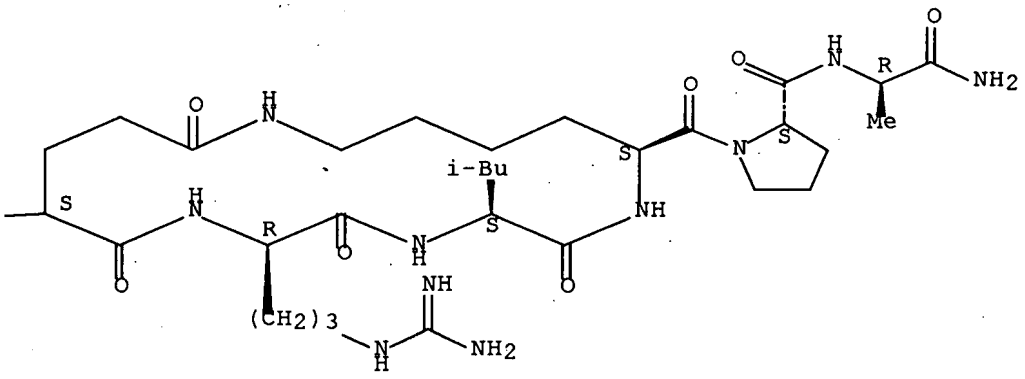
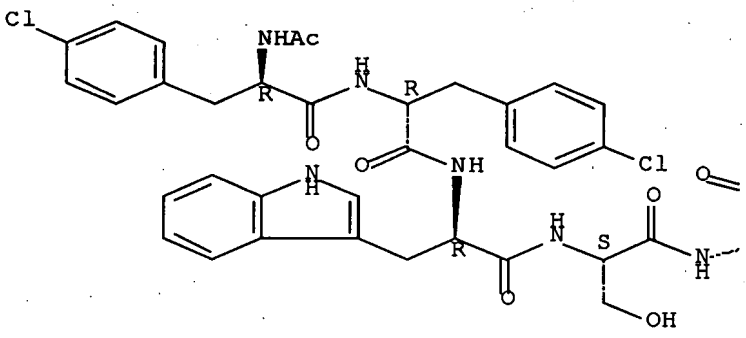


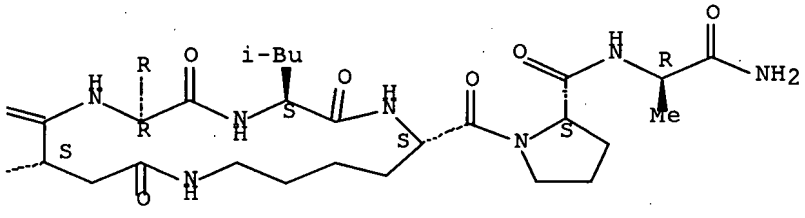
RN 121279-19-4 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-aspartyl-D-arginyl-L-leucyl-L-lysyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

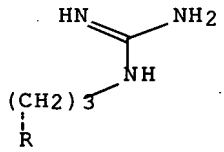
PAGE 1-A



PAGE 1-B



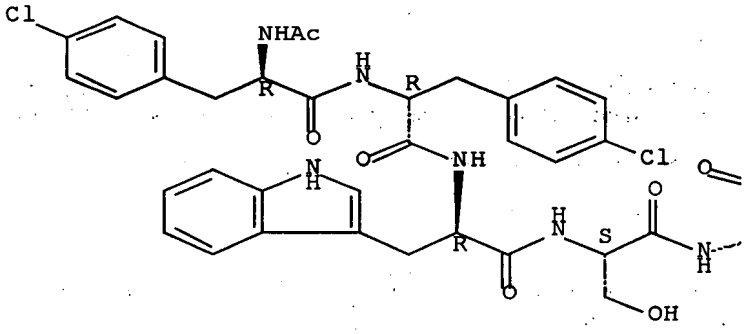
PAGE 2-A



RN 121279-26-3 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-ornithyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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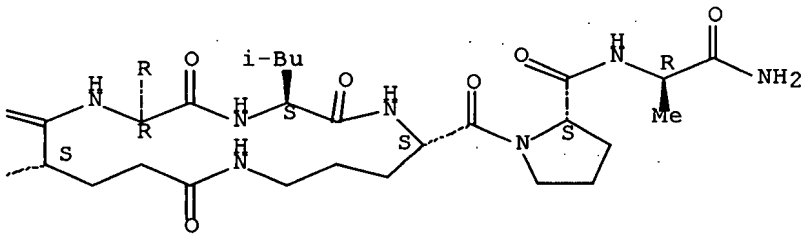

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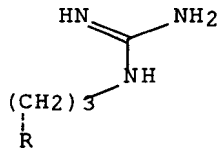
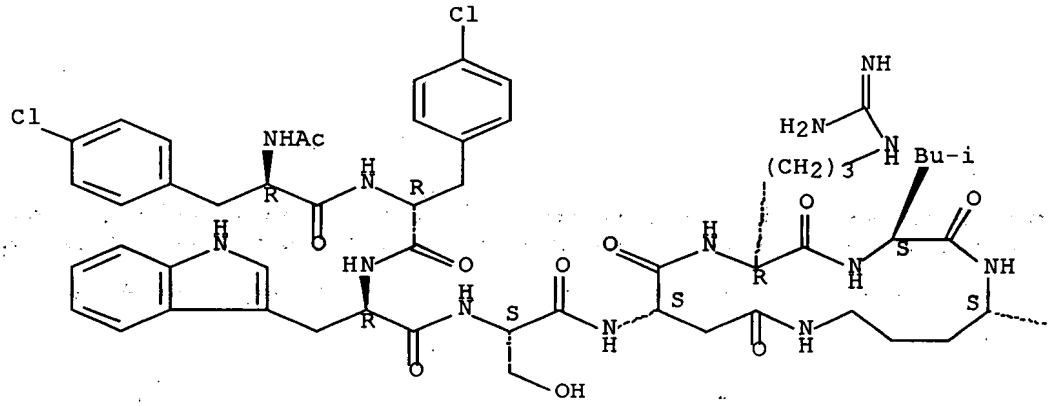


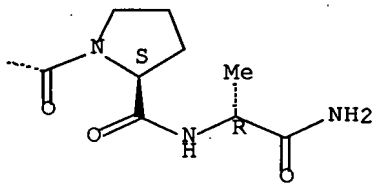
RN 121279-28-5 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-tryptophyl-L-seryl-L-α-aspartyl-D-arginyl-L-leucyl-L-ornithyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

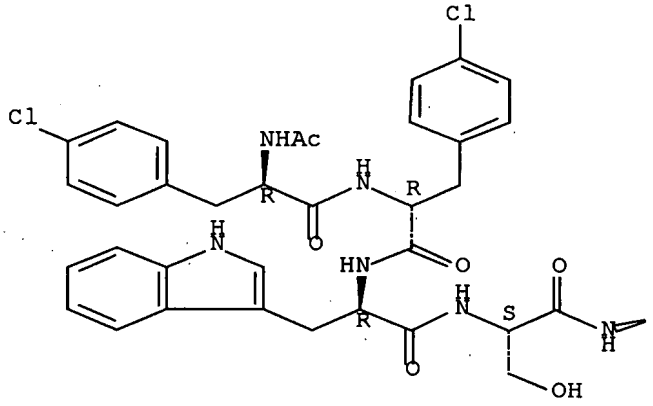


RN 121279-29-6 CAPLUS
CN D-Alaninamide, N-acetyl-4-chloro-D-phenylalanyl-4-chloro-D-phenylalanyl-D-

tryptophyl-L-seryl-L-α-glutamyl-D-arginyl-L-leucyl-L-2,4-diaminobutanoyl-L-prolyl-, cyclic (5→8)-peptide (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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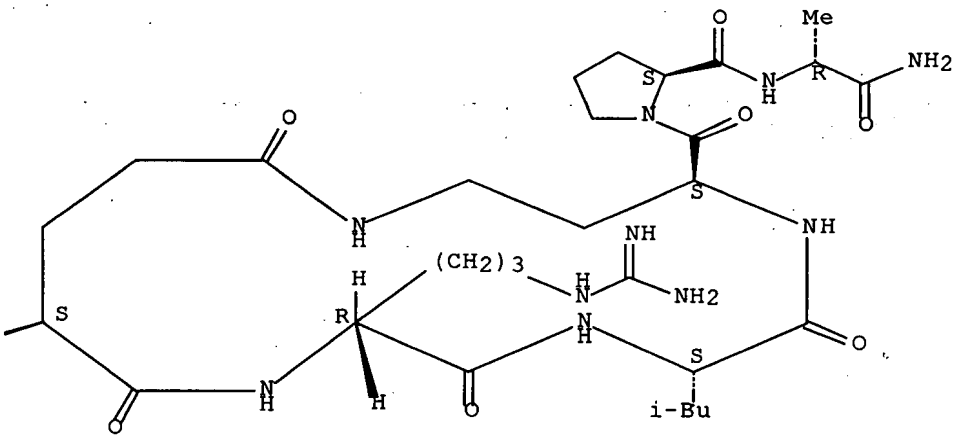

RN 121279-30-9 CAPLUS

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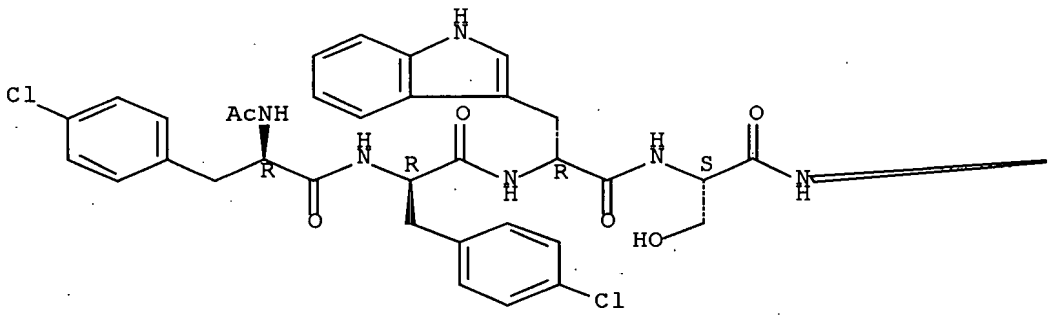
Absolute stereochemistry.

PAGE 1-A



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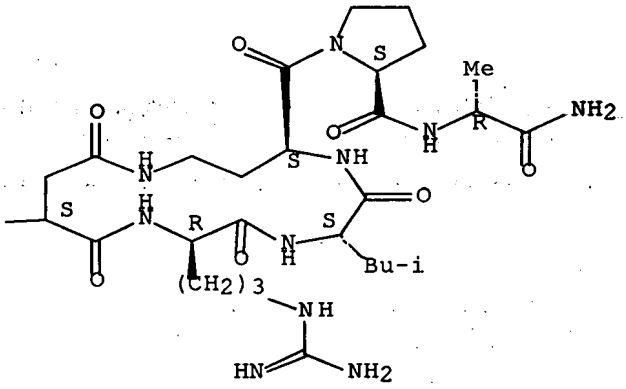

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